ANCHOR: melflufen plus dexamethasone and daratumumab or bortezomib in relapsed/refractory multiple myeloma: final results of a phase I/IIa study

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Supplementary data

Table of Contents

SUPPLEMENTARY METHODS

Eligibility criteria for both arms

Patients were considered eligible for inclusion if they met all of the following criteria:

1. Male or female, aged 18 years or older
2. A prior diagnosis of multiple myeloma with documented disease progression in need of treatment at time of screening
3. One to four prior lines of therapy
4. Measurable disease defined as any of the following:
    - Serum monoclonal protein ≥0.5 g/dL by serum protein electrophoresis
    - ≥200 mg/24 hours of monoclonal protein in the urine on 24-hour urine electrophoresis
    - Serum free light chain ≥10 mg/dL AND abnormal serum kappa to lambda free light chain ratio
5. Life expectancy of ≥6 months
6. Eastern Cooperative Oncology Group performance status ≤2 (patients with lower performance status based solely on bone pain secondary to multiple myeloma may be eligible following consultation and approval of the medical monitor)
7. Patient was a person of childbearing potential with a negative serum or urine pregnancy test prior to initiation of therapy and agreed to practice appropriate methods of birth control or was a person not of childbearing potential, or the patient was a male and agreed to practice appropriate methods of birth control
    - Person of childbearing potential is any sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (not having menstrual cycles due to cancer therapy does not rule out childbearing potential) for at least 24 consecutive months

8. Ability to understand the purpose and risks of the study and provided signed and dated informed consent
9. 12-lead electrocardiogram with QT interval calculated by Fridericia Formula (QTcF) interval of ≤470 msec
10. Adequate organ function with the following laboratory results during screening (within 21 days) and immediately before study drug administration on cycle 1 day 1:
    - Absolute neutrophil count ≥1000 cells/mm^3 (1.0×10^9/L) (Growth factors cannot be used within 10 days [14 days for pegfilgrastim] prior to initiation of therapy)
    - Platelet count ≥75,000 cells/mm^3 (75×10^9/L) (without required transfusions during the 10 days prior to initiation of therapy)
    - Hemoglobin ≥8.0 g/dL (red blood cell transfusions are permitted)
    - Total bilirubin ≤1.5 × upper limit of normal or patients diagnosed with Gilbert's syndrome, who have been reviewed and approved by the medical monitor
    - Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase and alanine aminotransferase/serum glutamic-pyruvic transaminase ≤3.0 × upper limit of normal
    - Renal function: Estimated creatinine clearance by Cockcroft-Gault formula ≥45 mL/min and serum creatinine ≤2 mg/dL
11. Must have had, or been willing to have, an acceptable central catheter (port-a-cath, peripherally inserted central catheter line, or central venous catheter)

Patients were ineligible for the study if they met any one of the following criteria:

1. Primary refractory disease (i.e., never responded with ≥ minimal response (MR) to any prior therapy)

2. Evidence of mucosal or internal bleeding and/or platelet transfusion refractory (i.e., platelet count fails to increase by >10,000 cells/mm^3 after transfusion of an appropriate dose of platelets)
3. Any medical conditions that, in the Investigator's opinion, would impose excessive risk to the patient or would adversely affect their participation in this study. Examples of such conditions are a significant history of cardiovascular disease (e.g., myocardial infarction, significant cardiac conduction system abnormalities, uncontrolled hypertension, grade ≥3 thromboembolic event in the past six months)
4. Known active infection requiring parenteral or oral anti-infective treatment within 14 days of initiation of therapy
5. Other malignancy diagnosed or requiring treatment within the past three years with the exception of adequately treated basal cell carcinoma, squamous cell skin cancer, carcinoma *in situ* of the cervix or breast, or very low and low-risk prostate cancer in active surveillance
6. Pregnant or breastfeeding females
7. Serious psychiatric illness, active alcoholism, or drug addiction that may hinder or confuse adherence or follow-up evaluation
8. Known human immunodeficiency virus or active hepatitis B or C viral infection (see criterion 5, additional requirements)
9. Concurrent symptomatic amyloidosis or plasma cell leukemia
10. POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
11. Previous cytotoxic therapies, including cytotoxic investigational agents, for multiple myeloma within three weeks (six weeks for nitrosoureas) prior to initiation of therapy. The use of live vaccines within 30 days before initiation of therapy; immunomodulatory agent, proteasome inhibitors (PIs), and/or corticosteroids within two weeks prior to

initiation of therapy. Other investigational therapies and monoclonal antibodies within four weeks of initiation of therapy. Prednisone up to but no more than 10 mg orally once daily or its equivalent for symptom management of comorbid conditions is permitted, but dose should be stable for at least seven days prior to initiation of therapy

12. Residual side effects to previous therapy grade >1 prior to initiation of therapy (alopecia any grade and/or neuropathy grade 1 without pain are permitted)
13. Prior peripheral stem cell transplant within 12 weeks of initiation of therapy
14. Prior allogeneic stem cell transplantation with active graft-versus-host-disease
15. Prior major surgical procedure or radiation therapy within four weeks of initiation of therapy (this does not include limited course of radiation used for management of bone pain within seven days of initiation of therapy)
16. Known intolerance to the required dose and schedule of steroid therapy as determined by the investigator
17. Prior treatment with melphalan flufenamide (melflufen)

Population diversity: This study was available to all eligible patients, regardless of race, gender, or ethnic origin. There was no information available regarding differential effects of these regimens in subsets defined by race, gender, or ethnicity, and there was no reason to expect such differences to exist. Investigators were encouraged to recruit a diverse population.

Regimen-specific eligibility criteria

Patients were eligible to receive therapy in the daratumumab regimen if they met the study eligibility criteria and

- Must have had a prior immunomodulatory agent and a PI, alone or in combination, and must have been refractory to (or intolerant of) an immunomodulatory agent, a PI, or both

    - Refractory was defined as failure to achieve ≥MR or progressed while on therapy or within 60 days of last dose
- Must not have had
    - Prior exposure to an anti-CD38 monoclonal antibody
    - Chronic obstructive pulmonary disease with forced expiratory volume in 1 second less than 50% of predicted normal
    - Moderate or severe persistent asthma within the two years prior to the study or had uncontrolled asthma of any classification at the time of study screening
    - Grade ≥3 conductive system abnormalities unless patient had a pacemaker
    - Active hepatitis B or been at risk for reactivation

Patients were eligible to receive therapy in the bortezomib arm of the study if they met the study inclusion/exclusion criteria and

- Must have had disease refractory to (or intolerant of) a prior Immunomodulatory agent
- Must not have had
    - Disease refractory to a PI in the last line of therapy prior to enrollment in the study (refractory was defined as failure to achieve ≥MR or progressed while on therapy or within 60 days of last dose)
    - History of allergic reaction/hypersensitivity attributed to compounds containing boron, mannitol, polysorbate 80, or sodium citrate dehydrate

Study design and patients

Each triplet combination began with a phase I component that followed the standard 3+3 phase I design with three to six patients at each dose level, depending on dose-limiting toxicity (DLT) observed in the first cycle of each patient. Patients who discontinue treatment during cycle 1 for

reasons other than study drug-related toxicity and/or were nonevaluable for DLT assessment were replaced at the discretion of the Data Safety Monitoring Committee. DLTs were defined as a grade 3 nonhematologic toxicity preventing the administration of >1 dose of daratumumab; grade 4 or higher nonhematologic toxicity; grade 4 thrombocytopenia (platelet count <25,000 cells/mm^3) preventing the administration of >1 dose of daratumumab or with clinically significant bleeding; grade 4 neutropenia (absolute neutrophil count <500 cells/mm^3) lasting >7 days; and/or >14-days' delay to meet the criteria for the start of a next cycle due to toxicity. The Data Safety Monitoring Committee evaluated all treated patients in each cohort prior to dose level adjustment recommendation.

The optimal dose of melflufen in combination therapy was defined as the highest of 30 mg or 40 mg of melflufen that resulted in at least one of six patients with DLTs during the first cycle of therapy. Once the optimal dose of melflufen had been determined for each combination regimen in phase I, approximately 20 additional efficacy-evaluable patients were enrolled in each combination regimen and treated at the dose determined in the phase I part of the study. Patients were assessed for response after each cycle according to the International Myeloma Working Group-Uniform Response Criteria. Patients who benefited from the therapy could continue treatment until disease progression or unacceptable toxicity or the patient/treating physician determined it was not in the patient's best interest to continue.

Dose modifications of melflufen for drug-related toxicity were permitted, including multiple dose reductions; however, the lowest dose permitted was 20 mg. Patients unable to tolerate melflufen 20 mg due to drug-related toxicity discontinued from treatment. Dose modifications for daratumumab were not recommended. Patients who discontinued treatment with melflufen, bortezomib, or daratumumab for any reason could continue treatment with the other drug in the regimen at the investigator's discretion if in the patients' best interest.

Patients who discontinued melflufen and continued treatment with the other drug in the regimen were followed for response, progression-free survival (PFS), and overall survival (OS) follow-up.

End-of-treatment visits were scheduled within 30 days after the last dose of study drug, followed by PFS assessments scheduled monthly until progressive disease or initiation of subsequent new therapy, and OS assessments were scheduled every three months.

Study endpoints

Primary endpoints

- Phase I: The primary endpoint of phase I was to analyze the frequency and grade of adverse events (AEs) occurring at each dose level to be tested during cycle 1 of therapy. Each treatment regimen and dose were evaluated separately
- Phase IIa: The primary endpoint of phase IIa was the overall response rate (ORR; defined as achieving stringent complete response [sCR], complete response [CR], very good partial response [VGPR], or partial response [PR]) observed in patients treated at the optimal dose of melflufen in combination therapy according to International Myeloma Working Group-Uniform Response Criteria. All response categories required two consecutive assessments made at any time before the initiation of a new therapy. Each treatment regimen and dose were evaluated separately

Secondary endpoints

Phase I and IIa:

- Best response during the study (sCR, CR, VGPR, PR, MR, stable disease, progressive disease, or nonevaluable)

- Clinical benefit rate (≥MR)
- Time to progression: Time from first dose to first documented confirmed progression; death from causes other than progression will be censored
- Time to response: Time from first dose or therapy to first documented confirmed response
- Time to next treatment: Time from date of initiation of therapy to start of next line of therapy
- Duration of response: Time (months) from the first evidence of confirmed assessment of sCR, CR, VGPR, or PR to first confirmed disease progression, or to death due to any cause. Duration of response is defined only for patients with a confirmed PR or better
- Duration of clinical benefit: time (months) from the first evidence of confirmed assessment of sCR, CR, VGPR, PR, or MR to first confirmed disease progression, or to death due to any cause. Duration of clinical benefit is defined only for patients with a confirmed MR or better
- PFS: Time (months) from date of initiation of therapy to the earlier of confirmed disease progression or death due to any cause or last known assessment
- OS: Time (months) from date of initiation of therapy to death due to any cause. Patients still alive at end of study or lost to follow-up will be censored at last day known alive
- The maximum grade (according to National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.03)[1] for each type of AE was recorded for each patient, and frequency tables were presented and reviewed to determine patterns. Additionally, the relationship of the AE(s) to the study treatment was taken into consideration
- Laboratory abnormalities were presented and reviewed

For safety analyses, each dose within each regimen was evaluated separately. For efficacy analyses, each regimen was evaluated separately, but dose levels were combined due to the small patient numbers.

Statistical analyses

In phase I, the sample size was determined by the number of dose levels evaluated within each regimen. In phase IIa, the sample size included patients from the phase I portion and approximately 20 additional efficacy-evaluable patients.

The safety analysis population comprised all patients who received at least one or a partial dose of melflufen, dexamethasone, or daratumumab and was the primary population for the efficacy, exposure, and safety data. The efficacy analysis population comprised all patients who received at least two doses of melflufen and ≥50% of daratumumab therapy during cycles 1 and 2, had a baseline disease assessment, and had at least one postbaseline disease assessment ≥28 days after first dose.

No formal statistical analysis was performed for the endpoints; each dose level was reported separately. The maximum grade for each AE was recorded for each patient, and frequency tables were presented and reviewed to determine patterns.

The exact 95% confidence interval (CI) for best response and clinical benefit rate was calculated for each dose. For PFS, the estimated 95% CIs were constructed using the Brookmeyer method,[2] with the duration of follow-up for PFS summarized according to the reverse Kaplan-Meier method.[3] Missing data were not estimated or carried forward for any other

summaries or analyses. If only a partial date was available and was required for a calculation, the date was assigned.

SUPPLEMENTARY REFERENCES

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SUPPLEMENTARY TABLES

Table S1. Patient disposition.

	Daratumumab arm[a]		Bortezomib arm[b]	
	Melflufen 30 mg (n=6)	**Melflufen 40 mg (n=27)**	**Melflufen 30 mg (n=15)**	**Melflufen 40 mg (n=8)**
Disposition				
On treatment at data cutoff	0	0	0	0
Discontinued treatment at data cutoff	6 (100)	27 (100)	15 (100)	8 (100)
Progressive disease	2 (33)	13 (48)	3 (20)	2 (25)
Adverse events	1 (17)	7 (26)	4 (27)	1 (13)
Study termination[c]	1 (17)	2 (7)	7 (47)	3 (38)
Lack of efficacy	1 (17)	2 (7)	0	1 (13)
Physician decision	0	2 (7)	0	0
COVID-19	1 (17)	0	1 (7)	1 (13)
Other	0	1 (4)	0	0

[a] In phase I, four patients total received melflufen 30 mg: three patients assigned to the 30-mg dose, and one patient who received 30 mg by error and was not evaluated for dose-limiting toxicity. An additional two patients received melflufen 30 mg in phase IIa due to a site error at the first dosing. [b] In phase I, six patients received melflufen 30 mg and were eligible for dose-limiting toxicity assessment, and seven patients received melflufen 40 mg, but only six patients were eligible for dose-limiting toxicity assessment (one patient received granulocyte colony-stimulating factor during cycle 1, which made them ineligible for dose-limiting toxicity assessment). [c] The study was prematurely terminated on February 23, 2022.

Table S2. Treatment-emergent adverse events (occurring in ≥10% of total patients) in the daratumumab arm.

	Overall (N=33)	**Melflufen 30 mg (n=6), n (%)**		**Melflufen 40 mg (n=27), n (%)**	
TEAEs in the daratumumab arm	**Any grade TEAE**	**Any grade TEAE**	**Grade ≥3 TEAE**	**Any grade TEAE**	**Grade ≥3 TEAE**
Any TEAE[a]	33 (100)	6 (100)	6 (100)	27 (100)	26 (96)
Thrombocytopenia[b]	29 (88)	6 (100)	5 (83)	23 (85)	23 (85)
Neutropenia[c]	26 (79)	6 (100)	5 (83)	20 (74)	19 (70)
Anemia	21 (64)	5 (83)	3 (50)	16 (59)	5 (19)
Fatigue	13 (39)	2 (33)	1 (17)	11 (41)	1 (4)
Upper respiratory tract infection	11 (33)	4 (67)	0	7 (26)	1 (4)
Diarrhea	10 (30)	1 (17)	0	9 (33)	0
Asthenia	9 (27)	2 (33)	1 (17)	7 (26)	0
Urinary tract infection	8 (24)	3 (50)	0	5 (19)	2 (7)
Infusion-related reaction	7 (21)	1 (17)	0	6 (22)	1 (4)

Nausea	7 (21)	0	0	7 (26)	0
Pyrexia	7 (21)	1 (17)	0	6 (22)	0
Back pain	6 (18)	2 (33)	1 (17)	4 (15)	0
Decreased appetite	6 (18)	2 (33)	0	4 (15)	0
Dyspepsia	6 (18)	1 (17)	0	5 (19)	0
Dyspnea	6 (18)	3 (50)	1 (17)	3 (11)	0
Insomnia	6 (18)	0	0	6 (22)	0
Arthralgia	5 (15)	0	0	5 (19)	0
Cough	5 (15)	1 (17)	0	4 (15)	0
Infection	5 (15)	3 (50)	0	2 (7)	1 (4)
Influenza	4 (12)	2 (33)	2 (33)	2 (7)	1 (4)
Peripheral edema	4 (12)	2 (33)	0	3 (11)	0
Respiratory tract infection	4 (12)	2 (33)	0	3 (11)	0
Bronchitis	4 (12)	1 (17)	0	3 (11)	0

Constipation	4 (12)	1 (17)	0	3 (11)	0
Fall	4 (12)	2 (33)	1 (17)	2 (7)	0
Hypokalemia	4 (12)	1 (17)	1 (17)	3 (11)	1 (4)
Nasopharyngitis	4 (12)	3 (50)	0	1 (4)	0
Pneumonia	4 (12)	1 (17)	1 (17)	3 (11)	2 (7)
Vomiting	4 (12)	1 (17)	0	4 (15)	0

[a] TEAEs were coded to preferred term using MedDRA, version 24.0. [b] Thrombocytopenia includes the preferred terms "thrombocytopenia" and "platelet count decreased" pooled together. [c] Neutropenia includes the preferred terms "neutropenia" and "neutrophil count decreased" pooled together. TEAE: treatment-emergent adverse event.

Table S3. Treatment exposure.

	Daratumumab arm[a]		**Bortezomib arm[b]**	
	Melflufen 30 mg (n=6)	**Melflufen 40 mg (n=27)**	**Melflufen 30 mg (n=15)**	**Melflufen 40 mg (n=8)**
Treatment exposure, median (range)				
Number of treatment cycles	21.5 (1-45)	6.0 (1-41)	8.0 (3-35)	9.5 (2-31)
Treatment duration, months	24.2 (0.9-44.7)	6.2 (0.9-41.2)	8.2 (2.9-40.0)	11.8 (2.1-34.7)
Total cumulative dose administered, mg (range)				
Melflufen	334 (30-1350)	150 (40-870)	210 (90-940)	225 (80-1240)
Daratumumab	46,315 (5670-97,264)	16,128 (3776-62,576)	NA	NA
Bortezomib	NA	NA	54 (18-252)	66 (12-163)
Relative dose intensity, %[c]				
Melflufen	85 (55-100)	92 (60-100)	95 (73-100)	79 (59-100)
Daratumumab	97 (75-100)	98 (63-102)	NA	NA
Bortezomib	NA	NA	63 (53-86)	62 (52-81)

Cycle delays				
Interval between doses while on starting melflufen dose, median (range), days	35 (26-48)	28 (26-57)	28 (26-63)	35 (28-83)
Patients with ≥1 prolonged cycle of ≥32 days duration when on starting melflufen dose, n (%)	5 (83)	21 (78)	11 (73)	8 (100)
Patients with ≥1 prolonged cycle of ≥39 days duration when on starting melflufen dose, n (%)	4 (67)	18 (67)	6 (40)	5 (63)
Patients with a prolonged treatment cycle in their first cycle, n (%)[d]	4 (67)	8 (30)	5 (33)	5 (63)
Patients with a hematologic toxicity preventing initiation of cycle 2, n (%)	2 (33)	7 (26)	1 (7)	3 (38)

[a] In phase 1, four patients total received melflufen 30 mg: three patients assigned to the 30-mg dose, and one patient who received 30 mg by error and was not evaluated for dose-limiting toxicity. An additional two patients received melflufen 30 mg in phase IIa due to a site error at the first dosing. [b] In phase I, six patients received melflufen 30 mg and were eligible for dose-limiting toxicity assessment, and seven patients received melflufen 40 mg, but only six patients were eligible for dose-limiting toxicity assessment (one patient received granulocyte colony-stimulating factor during cycle 1, which made them ineligible for dose-limiting toxicity assessment). [c] Relative dose intensity was calculated as: total cumulative dose administered of drug/total planned dose×100. [d] A prolonged treatment cycle was defined as a cycle duration >31 days.

Table S4. Treatment-emergent adverse events leading to melflufen dose interruptions, dose reductions, and discontinuations.

	Daratumumab arm		Bortezomib arm	
	Melflufen 30 mg (n=6)	**Melflufen 40 mg (n=27)**	**Melflufen 30 mg (n=15)**	**Melflufen 40 mg (n=8)**
TEAEs leading to melflufen dose interruption, n (%)[a]	6 (100)	23 (85)	11 (73)	8 (100)
Thrombocytopenia[b]	4 (67)	19 (70)	5 (33)	7 (88)
Neutropenia[c]	3 (50)	7 (26)	3 (20)	3 (38)
Infection	2 (33)	1 (4)	2 (13)	2 (25)
Upper respiratory tract infection	2 (33)	1 (4)	3 (20)	2 (25)
Anemia	0	3 (11)	2 (13)	1 (13)
Pneumonia	1 (17)	1 (4)	2 (13)	1 (13)
COVID-19	1 (17)	0	1 (7)	2 (25)
SARS-CoV-2 test positive	0	0	2 (13)	2 (25)
TEAEs leading to melflufen dose reduction, n (%)[a]	3 (50)	19 (70)	8 (53)	6 (75)
Thrombocytopenia[b]	2 (33)	16 (59)	5 (33)	6 (75)

Neutropenia[c]	1 (17)	7 (26)	1 (7)	1 (13)
Number of cycles before first melflufen dose reduction, median (range)	5.0 (1-5)	3.0 (1-12)	4.5 (1-28)	2.0 (1-6)
Number of cycles after first melflufen dose reduction, median (range)	9.0 (1-15)	2.0 (1-19)	5.0 (3-18)	5.5 (2-16)
TEAEs leading to melflufen treatment discontinuation, n (%)[d]	3 (50)	15 (56)	5 (33)	4 (50)
Thrombocytopenia[b]	1 (17)	11 (41)	1 (7)	2 (25)
Neutropenia[c]	0	2 (7)	0	0
Anemia	0 (0)	2 (7)	0	0
COVID-19 pneumonia	0	0	1 (7)	1 (13)

[a] Most common TEAEs leading to melflufen dose interruptions or reductions occurring in at least four patients overall in either treatment arm. [b] Thrombocytopenia includes the preferred terms “thrombocytopenia” and “platelet count decreased.” [c] Neutropenia includes the preferred terms “neutropenia” and “neutrophil count decreased.” [d] Most common TEAEs leading to treatment discontinuation occurring in at least two patients overall in either treatment arm. TEAE: treatment-emergent adverse event.

Table S5. Treatment-emergent adverse events (occurring in ≥10% of total patients) in the bortezomib arm.

TEAEs in the bortezomib arm	Overall (N=23)	Melflufen 30 mg (n=15), n (%)		Melflufen 40 mg (n=8), n (%)	
	Any grade TEAE	Any grade TEAE	Grade ≥3 TEAE	Any grade TEAE	Grade ≥3 TEAE
Any TEAE[a]	23 (100)	15 (100)	15 (100)	8 (100)	8 (100)
Thrombocytopenia[b]	21 (91)	13 (87)	12 (80)	8 (100)	8 (100)
Neutropenia[c]	18 (78)	11 (73)	5 (33)	7 (88)	6 (75)
Anemia	16 (70)	10 (67)	5 (33)	6 (75)	5 (62)
Fatigue	7 (30)	5 (33)	2 (13)	2 (25)	0
Infection	7 (30)	4 (27)	0	3 (38)	1 (13)
Diarrhea	6 (26)	5 (33)	1 (7)	1 (13)	1 (13)
Nausea	6 (26)	4 (27)	0	2 (25)	0
Upper respiratory tract infection	6 (26)	4 (27)	0	2 (25)	0
Asthenia	5 (22)	4 (27)	0	1 (13)	0

Urinary tract infection	5 (22)	3 (20)	0	2 (25)	1 (13)
Arthralgia	4 (17)	3 (20)	0	1 (13)	0
COVID-19	4 (17)	2 (13)	0	2 (25)	0
Hypokalemia	4 (17)	2 (13)	0	2 (25)	0
Pneumonia	4 (17)	3 (20)	1 (7)	1 (13)	0
Polyneuropathy	4 (17)	3 (20)	0	1 (13)	0
Back pain	3 (13)	3 (20)	2 (13)	0	0
COVID-19 pneumonia	3 (13)	2 (13)	2 (13)	1 (13)	1 (13)
C-reactive protein increase	3 (13)	1 (7)	1 (7)	2 (25)	0
Dyspnea	3 (13)	3 (20)	1 (7)	0	0
Fall	3 (13)	2 (13)	0	1 (13)	0
Hypotension	3 (13)	3 (20)	1 (7)	3 (38)	0
Pyrexia	3 (13)	2 (13)	0	1 (13)	0
Soft tissue infection	3 (13)	0	0	3 (38)	0

[a] TEAEs were coded to preferred term using MedDRA, version 24.0.[b] Thrombocytopenia includes the preferred terms "thrombocytopenia" and "platelet count decreased" pooled together. [c] Neutropenia includes the preferred terms "neutropenia" and "neutrophil count decreased" pooled together. TEAE: treatment-emergent adverse event.

SUPPLEMENTARY FIGURES

Figure S1. Best M-protein response with melflufen, daratumumab, and dexamethasone. Best percentage change from baseline in M-protein based on type of measurable disease for 33 patients with M-protein assessments at baseline and at least one postbaseline assessment. An asterisk (*) denotes patients with unconfirmed responses. CR: complete response; F: free light chains, MR: minimal response; NE, not evaluable; PD: progressive disease; PR: partial response; sCR: stringent complete response; S: serum, SD: stable disease; U: urine; VGPR: very good partial response.

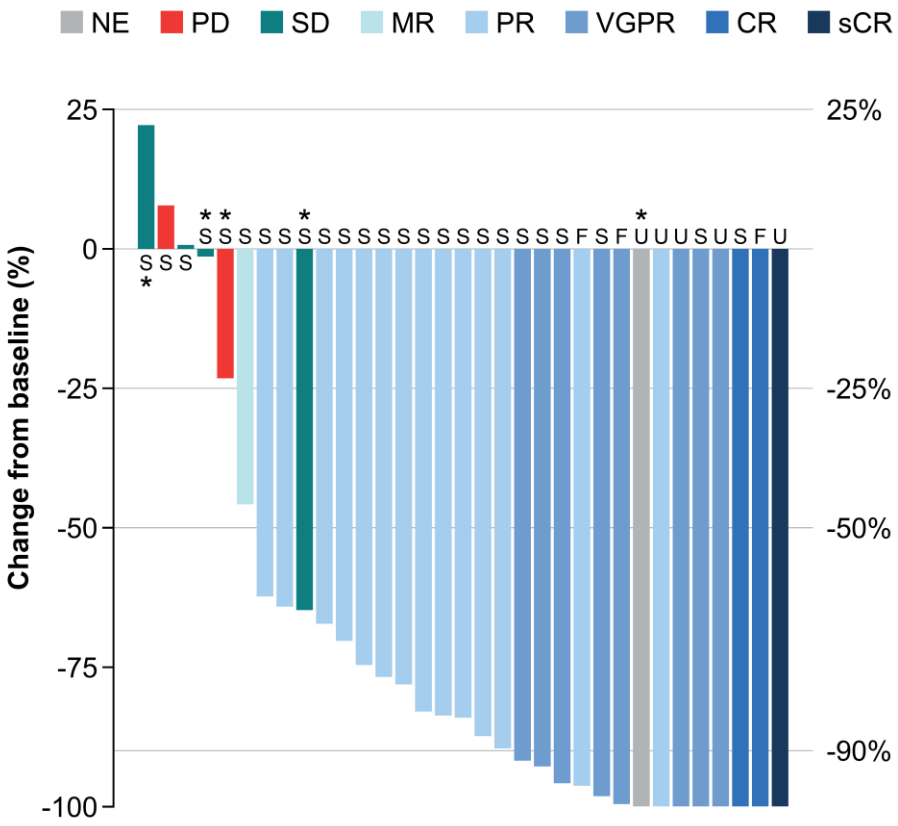

Figure S2. Duration of response with melflufen, daratumumab, and dexamethasone.

Data for 24 patients who achieved a partial response or better with melflufen, daratumumab, and dexamethasone. Open circle denotes last melflufen dose received; X denotes occurrence of progression-free survival event; blunt arrow indicates study termination. CR: complete response; MR: minimal response; PR: partial response; sCR: stringent complete response; SD: stable disease; VGPR: very good partial response.

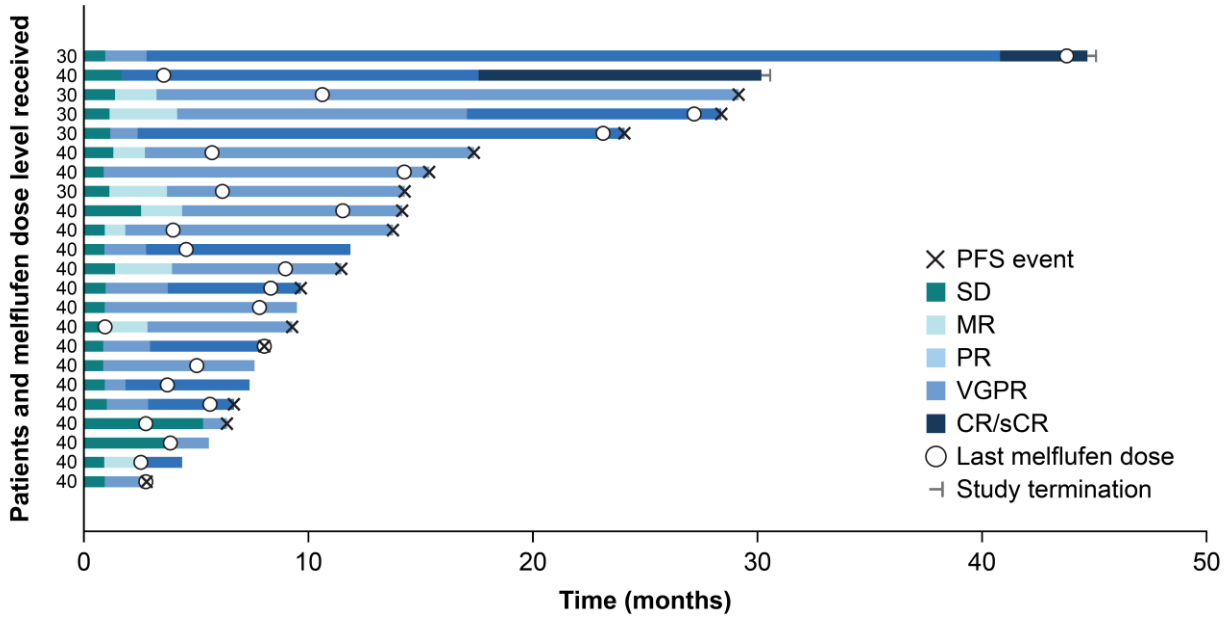

Figure S3. Best M-protein response with melflufen, bortezomib, and dexamethasone.

Best percentage change from baseline in M-protein based on type of measurable disease for 23 patients with M-protein assessments at baseline and at least one postbaseline assessment. An asterisk (*) denotes patient with unconfirmed response. CR: complete response; F: free light chains, MR: minimal response; PD: progressive disease; PR: partial response; sCR: stringent complete response; S: serum, SD: stable disease; U: urine; VGPR: very good partial response.

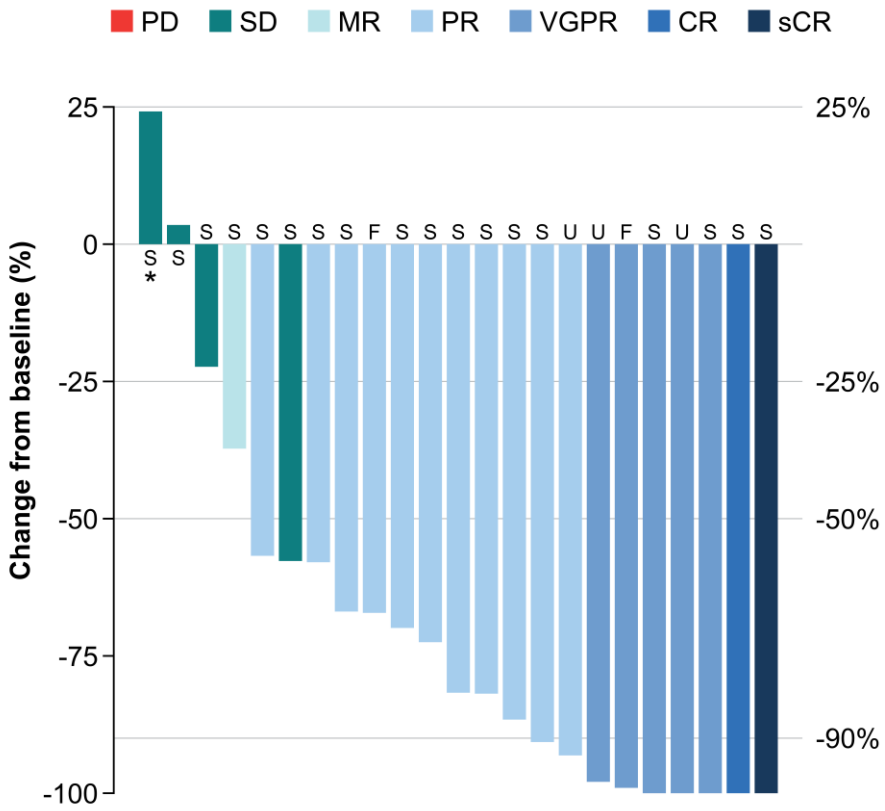

Figure S4. Duration of response with melflufen, bortezomib, and dexamethasone.

Data for 18 patients who achieved a partial response or better with melflufen, bortezomib, and dexamethasone. Open circle denotes last melflufen dose received; X denotes occurrence of progression-free survival event; blunt arrow indicates study termination. CR: complete response; MR: minimal response; PFS: progression-free survival; PR: partial response; sCR: stringent complete response; SD: stable disease; VGPR: very good partial response.