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Belantamab Mafodotin, Bortezomib, and Dexamethasone for Multiple Myeloma

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ABSTRACT

BACKGROUND

Belantamab mafodotin had single-agent activity in patients with relapsed or refractory multiple myeloma, a finding that supports further evaluation of the agent in combination with standard-care therapies.

METHODS

In this phase 3, open-label, randomized trial, we evaluated belantamab mafodotin, bortezomib, and dexamethasone (BVd), as compared with daratumumab, bortezomib, and dexamethasone (DVd), in patients who had progression of multiple myeloma after at least one line of therapy. The primary end point was progression-free survival. Key secondary end points were overall survival, response duration, and minimal residual disease (MRD)–negative status.

RESULTS

In total, 494 patients were randomly assigned to receive BVd (243 patients) or DVd (251 patients). At a median follow-up of 28.2 months (range, 0.1 to 40.0), median progression-free survival was 36.6 months (95% confidence interval [CI], 28.4 to not reached) in the BVd group and 13.4 months (95% CI, 11.1 to 17.5) in the DVd group (hazard ratio for disease progression or death, 0.41; 95% CI, 0.31 to 0.53; P<0.001). Overall survival at 18 months was 84% in the BVd group and 73% in the DVd group. An analysis of the restricted mean response duration favored BVd over DVd (P<0.001). A complete response or better plus MRD-negative status occurred in 25% of the patients in the BVd group and 10% of those in the DVd group. Grade 3 or higher adverse events occurred in 95% of the patients in the BVd group and 78% of those in the DVd group. Ocular events were more common in the BVd group than in the DVd group (79% vs. 29%); such events were managed with dose modifications, and events of worsening visual acuity mostly resolved.

CONCLUSIONS

As compared with DVd therapy, BVd therapy conferred a significant benefit with respect to progression-free survival among patients who had relapsed or refractory multiple myeloma after at least one line of therapy. Most patients had grade 3 or higher adverse events. (Funded by GSK; DREAMM-7 ClinicalTrials.gov number, NCT04246047; EudraCT number, 2018-003993-29.)

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*A list of the DREAMM-7 Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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CME

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Patients with multiple myeloma are treated initially with triplet or quadruplet combination regimens that include proteasome inhibitors, immunomodulators, and anti-CD38 monoclonal antibodies.[1-3] Most patients have disease progression after initial treatment, which highlights the need for efficacious second-line combinations that incorporate new therapeutics.[4,5]

B-cell maturation antigen (BCMA) is an established target for the treatment of multiple myeloma.[6] Belantamab mafodotin is a BCMA-targeting antibody–drug conjugate with diverse mechanisms of antitumor activity.[7-12] We report results from the DREAMM-7 trial, which is evaluating the efficacy and safety of belantamab mafodotin, bortezomib, and dexamethasone (BVd), as compared with daratumumab, bortezomib, and dexamethasone (DVd), in patients with relapsed or refractory multiple myeloma.

Methods

Patients, Treatment, and Oversight

We are conducting an ongoing phase 3, open-label, global, randomized trial involving patients with multiple myeloma who had received at least one line of therapy and had had disease progression during or after the most recent therapy. Patients were excluded from the trial if they had disease that was refractory to anti-CD38 therapy or had had exposure to anti-BCMA therapy. Details regarding the eligibility criteria are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Patients were randomly assigned in a 1:1 ratio to receive either BVd or DVd (Fig. S1 in the Supplementary Appendix). Randomization was performed centrally. Both treatment groups were to receive bortezomib (administered subcutaneously at a dose of 1.3 mg per square meter of body-surface area on days 1, 4, 8, and 11 of 21-day cycles) and dexamethasone (administered orally or intravenously at a dose of 20 mg on the day of and the day after bortezomib administration) for the first eight cycles. The BVd group was to receive belantamab mafodotin (administered intravenously at a dose of 2.5 mg per kilogram of body weight on day 1 of 21-day cycles [every 3 weeks]) until the occurrence of disease progression. The belantamab mafodotin dose could be reduced to 1.9 mg per kilogram or delayed to manage adverse events. The DVd group was to receive daratumumab (administered intravenously at a dose of 16 mg per kilogram every week in cycles 1 through 3, every 3 weeks in cycles 4 through 8, and every 4 weeks in cycle 9 and beyond) until the occurrence of disease progression. Treatment was continued until the occurrence of progressive disease, unacceptable toxic effects, withdrawal of consent, or death (whichever occurred first). Patients were stratified according to Revised International Staging System stage at screening (I vs. II or III), previous exposure to bortezomib (yes vs. no), and the number of previous lines of therapy (one vs. two or three vs. four or more). Up to 50% of the patients enrolled could have received two or more previous lines of therapy. Crossover between treatment groups was not permitted.

The trial was sponsored by GSK. Company representatives were involved in the collection, analysis, and interpretation of the data. The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All the patients provided written informed consent before enrollment. The trial protocol and amendments (available at NEJM.org) were approved by the appropriate ethics body at each participating institution. Medical writing assistance, under the direction of the authors, was funded by GSK. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

End Points and Assessments

The primary end point was progression-free survival, defined as the time from randomization to the occurrence of documented disease progression or death from any cause. Disease progression was assessed by an independent review committee with the use of International Myeloma Working Group criteria.[13] A post hoc supplementary analysis was performed in which any occurrence of disease progression or death was considered to be an event, regardless of whether the patient had started a new antimyeloma therapy or had extended loss to follow-up. Key secondary end points were overall survival, response duration, and minimal residual disease (MRD)–negative status, which was assessed by means of next-generation sequencing at a sensitivity of 10^{-5} or lower. Additional secondary end points were adverse events, which were graded in accordance with

the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0, and findings on ocular examination, which were graded with the use of the Keratopathy and Visual Acuity (KVA) scale. The KVA grade is a composite grade that is based on findings on corneal examination and changes in the best corrected visual acuity (BCVA).[14] In the BVd group, an ocular examination was performed at screening, every 3 weeks before treatment administration up to at least the sixth dose of belantamab mafodotin, and then every 3 months if there were no ocular findings. In the DVd group, an ocular examination was performed at screening, at cycle 6, and then every 6 months. To assess the change from baseline in health-related quality of life, the scores on the global health status and quality-of-life domains of the European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire were obtained at each visit. Details regarding the end points and assessments are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

The sample size was driven by the analysis of the primary end point, progression-free survival. We estimated that a sample of approximately 478 patients, with approximately 280 events (disease progression or death) in the intention-to-treat population, would provide the trial with approximately 92% power to detect a significant difference between the BVd group and the DVd group in progression-free survival, at a one-sided significance level of 2.5%. The estimate was based on an assumed hazard ratio for disease progression or death of 0.67. One interim analysis of progression-free survival was to be performed when approximately 250 events had occurred. The familywise type I error was controlled at 2.5% (one-sided) across hypotheses for progression-free survival, overall survival, response duration, and MRD-negative status (Fig. S2); for the interim and final analyses of progression-free survival and overall survival, efficacy boundaries were defined with the Lan–DeMets O'Brien–Fleming spending function (Table S1).

Progression-free survival and overall survival were compared between treatment groups with a stratified log-rank test. Hazard ratios and corresponding 95% confidence intervals were estimated with a stratified Cox proportional-hazards model, with treatment as the only explanatory variable. The Kaplan–Meier method was used to estimate the median progression-free survival and overall survival; corresponding 95% confidence intervals were calculated with the Brookmeyer–Crowley method. The methods used in the primary analysis incorporate the missing-at-random assumption, which specifies that missingness does not depend on the unobserved data. A stratified Cochran–Mantel–Haenszel test was used in the analysis of MRD-negative status. The main analysis of response duration involved the use of the restricted mean response duration.[15] A conventional analysis of response duration, involving a method similar to that used for progression-free survival and overall survival, was performed as a sensitivity analysis. Prespecified subgroup analyses of progression-free survival were performed (Table S2).

Results are reported from the successful interim analysis for progression-free survival, which was performed after 249 events had occurred (data cutoff, October 2, 2023). This interim analysis was performed with a multiplicity-adjusted boundary for significance of $P<0.017$. The boundary was one-sided according to the statistical analysis plan; two-sided P values are reported (Table S3). The two-sided (alpha level, 0.05) 95% confidence intervals reported were not adjusted for multiplicity and cannot be used in place of hypothesis testing to infer definitive treatment effects. Details regarding the statistical analysis are provided in the Supplementary Appendix.

RESULTS

PATIENTS AND TREATMENT

From May 7, 2020, through June 28, 2021, a total of 494 patients were randomly assigned to receive BVd (243 patients) or DVd (251 patients); these patients were included in the intention-to-treat population. At the time of the data cutoff, all the patients were in the monotherapy phase. Overall, 81 of the 243 patients (33%) in the BVd group and 51 of the 251 patients (20%) in the DVd group were receiving the trial treatment (Fig. S3); 161 patients (66%) had discontinued belantamab mafodotin, and 195 patients (78%) had discontinued daratumumab. One patient in the BVd group and 5 patients in the DVd group had undergone randomization but had not received the trial treatment. Progressive disease was the most common reason for discontinuation of

belantamab mafodotin or daratumumab; 24% of the patients in the BVd group had discontinued belantamab mafodotin and 59% in the DVd group had discontinued daratumumab for this reason (Table S4).

The trial population was closely representative of the population of patients with multiple myeloma in terms of the sex and age distribution. However, the trial population had more White patients than patients in other racial groups, with an underrepresentation of Black patients (Table S5). The characteristics of the patients and previous treatments at baseline were well balanced between the treatment groups (Table 1). Overall, 250 of the 494 patients (51%) had received one previous line of therapy, 257 (52%) had had exposure to lenalidomide, 166 (34%) had disease that was refractory to lenalidomide (Table S6), and 136 (28%) had high cytogenetic risk.

EFFICACY

At a median follow-up of 28.2 months (range, 0.1 to 40.0), median progression-free survival was 36.6 months (95% confidence interval [CI], 28.4 to not reached [NR]) in the BVd group and 13.4 months (95% CI, 11.1 to 17.5) in the DVd group (hazard ratio for disease progression or death, 0.41; 95% CI, 0.31 to 0.53; P<0.001) (Fig. 1A). Of the 249 total events (disease progression or death), 91 (37%) had occurred in the BVd group and 158 (63%) had occurred in the DVd group. The investigators and the independent review committee were largely in agreement in their assessment of progressive disease (Table S7). A post hoc analysis showed that follow-up for patients with censored data was balanced between the treatment groups (Table S9). The results of prespecified subgroup analyses of progression-free survival are shown in Figure S4. The results of a post hoc supplementary analysis in which any occurrence of disease progression or death was considered to be an event, regardless of whether the patient had started a new antimyeloma therapy or had extended loss to follow-up, are shown in Figure 1B. The results of further supplementary analyses were all consistent with the results of the primary analysis (Tables S10 and S11).

At the time of the data cutoff, 54 patients (22%) in the BVd group and 87 patients (35%) in the DVd group had died. Overall survival at 18 months was 84% in the BVd group and 73% in the DVd group (Fig. 2). The 25th percentile of the distribution of overall survival was 33.9 months (95% CI, 21.9 to NR) in the BVd group and 15.2 months (95% CI, 12.3 to 21.1) in the DVd group. At the data cutoff, the results for overall survival did not meet the significance criterion; follow-up for overall survival is ongoing.

The percentage of patients who had a response to treatment (partial response or better) was 83% (95% CI, 77 to 87) in the BVd group and 71% (95% CI, 65 to 77) in the DVd group (Table 2 and Fig. S5). The depth of response was greater with BVd than with DVd; 35% of the patients in the BVd group had a complete response or better, as compared with 17% of the patients in the DVd group. A complete response or better plus MRD-negative status occurred in 25% of the patients in the BVd group and 10% of those in the DVd group. The median response duration was 35.6 months (95% CI, 30.5 to NR) in the BVd group and 17.8 months (95% CI, 13.8 to 23.6) in the DVd group; the 25th percentile of the distribution of response duration was 18.8 months (95% CI, 13.2 to 23.5) in the BVd group and 9.0 months (95% CI, 6.4 to 10.4) in the DVd group (Fig. S6). However, because more than half the responses in the BVd group were still ongoing at the time of the interim analysis, the data regarding the median response duration were not fully mature. A separate analysis of the restricted mean response duration favored BVd over DVd (P<0.001); details are provided in the Supplementary Appendix.

The most common therapies administered after DVd were glucocorticoids, immunomodulators, and proteasome inhibitors; the most common therapies administered after BVd were glucocorticoids, immunomodulators, and monoclonal antibodies. In a post hoc analysis, among the 110 patients in the DVd group who had received any subsequent antimyeloma therapy, the first treatment after DVd was lenalidomide in 32 patients (29%), carfilzomib in 30 (27%), pomalidomide in 24 (22%), and belantamab mafodotin in 15 (14%). Among the 62 patients in the BVd group who had received any subsequent antimyeloma therapy, the first treatment after BVd was daratumumab in 25 patients (40%), pomalidomide in 18 (29%), and lenalidomide in 13 (21%). The benefits of treatment with BVd

were maintained, as shown by the time to the occurrence of disease progression or death from any cause after subsequent antimyeloma therapy (Table S12).

Among the 67 patients in the BVd group who had disease progression, 36 had samples available for a post hoc analysis of soluble BCMA levels. All 36 patients had detectable soluble BCMA at baseline and at the time of disease progression. For the 32 patients with available soluble BCMA data who had a confirmed response, the analysis showed that soluble BCMA levels were numerically lower than baseline levels while the patients were having a response (median relative decrease from baseline, 78%) but increased when disease progression occurred (Fig. S7). This finding, which suggests that there was no BCMA target loss, is similar to previously reported findings.[16]

SAFETY

The safety population included the 488 patients (242 in the BVd group and 246 in the DVd group) who had received at least one dose of any trial drug. The median duration of exposure to any trial drug was 15.9 months (range, 0.7 to 40.2) in the BVd group and 12.9 months (range, 0.2 to 40.5) in the DVd group. All the patients had at least one adverse event (Table 3). Grade 3 or higher adverse events occurred in 95% of the patients in the BVd group and 78% of those in the DVd group, and serious adverse events occurred in 50% and 37%, respectively (Table S13).

Discontinuation of any trial drug due to adverse events that were considered by the investigator to be related to treatment occurred in 64 patients (26%) in the BVd group and 36 patients (15%) in the DVd group. The following adverse events led to discontinuation of any trial drug in at least 2% of the patients in either treatment group: peripheral sensory neuropathy (5% in the BVd group and 2% in the DVd group), peripheral neuropathy (2% and 4%, respectively), polyneuropathy (3% and 2%), pneumonia (4% and none), coronavirus disease 2019 (Covid-19) (1% and 2%), Covid-19 pneumonia (<1% and 2%), thrombocytopenia (2% and <1%), and blurred vision (2% and none) (Table S13). In addition, 23 patients (10%) in the BVd group and 19 patients (8%) in the DVd group died from serious adverse events; the serious adverse event that led to death was considered to be related to treatment in 7 patients (3%) and 2 patients (1%), respectively (Table S14).

In both treatment groups, the most common adverse events according to system organ class were blood disorders and infections. Although the incidence of thrombocytopenia was higher in the BVd group than in the DVd group (69% vs. 50%), there was no substantial difference between the treatment groups in the percentage of patients with a concomitant grade 3 or 4 platelet-count decrease and grade 2, 3, or 4 bleeding event (7% with BVd and 6% with DVd). The incidence of anemia was 19% in the BVd group and 26% in the DVd group. The incidence of infections was similar in the two groups (70% with BVd and 67% with DVd), although grade 3 or higher pneumonia was more common in the BVd group than in the DVd group (12% vs. 4%). Data regarding opportunistic infections were not collected systematically; however, when an analysis was performed with the use of the adverse-event terms "aspergillus infection," "cytomegalovirus reactivation," and "pneumonia fungal," the incidence of these three opportunistic infections was low and balanced between the treatment groups (<1% in each group). In a post hoc analysis, immunoglobulin replacement was more common with BVd than with DVd (8% vs. 4%) (Table S13). Other nonocular adverse events that occurred in at least 20% of the patients in either treatment group included diarrhea, peripheral sensory neuropathy, peripheral neuropathy, constipation, and fatigue.

Because belantamab mafodotin has known ocular toxic effects, patients underwent regular ocular assessments. Ocular adverse events were more common in the BVd group than in the DVd group (any grade, 79% vs. 29%; grade 3 or 4, 34% vs. 3%). The most common grade 3 or 4 ocular adverse events with BVd were blurred vision, dry eyes, and cataract, whereas cataract was the most common with DVd.

Changes on corneal examination are summarized in the Supplementary Methods. Among the patients with a normal BCVA (defined as 20/25 or better in at least one eye) at baseline, a decrease in the BCVA to 20/50 or worse in both eyes occurred in 34%, and a decrease to 20/200 in both eyes occurred in 2% (Table 4). In 98% of the patients who had a decrease to 20/50 in both eyes, and in all the patients who had a decrease to 20/200 in both eyes, the BCVA improved after

Table 1. Baseline Demographic and Clinical Characteristics and Previous Therapies.*

Characteristics	BVd (N=243)	DVd (N=251)
Median age (range) — yr	65.0 (34.0–86.0)	64.0 (32.0–89.0)
Age category — no. (%)		
18 to <65 yr	121 (50)	126 (50)
65 to <75 yr	85 (35)	95 (38)
≥75 yr	37 (15)	30 (12)
Sex — no. (%)		
Male	128 (53)	144 (57)
Female	115 (47)	107 (43)
Race — no. (%)†		
White	206 (85)	203 (81)
Black	8 (3)	12 (5)
Asian	28 (12)	33 (13)
ECOG performance-status score ≤1 — no./total no. (%)‡	232/242 (96)	235/246 (96)
R-ISS stage at screening — no. (%)		
I	102 (42)	103 (41)
II	130 (53)	132 (53)
III	9 (4)	14 (6)
Unknown	2 (1)	2 (1)
Median time since diagnosis (range) — yr	4.3 (0.2–26.0)	3.9 (0.1–23.4)
Cytogenetic risk — no. (%)§		
Standard	175 (72)	175 (70)
High	67 (28)	69 (27)
t(4;14)	41 (17)	42 (17)
t(14;16)	8 (3)	6 (2)
del(17p13)	30 (12)	35 (14)
Missing or not evaluable	1 (<1)	7 (3)
Other cytogenetic abnormalities — no. (%)		
del(13)	18 (7)	28 (11)
del(1p)	22 (9)	31 (12)
Hyperdiploidy	33 (14)	28 (11)
t(11;14)	13 (5)	15 (6)
t(14;20)	1 (<1)	1 (<1)
1q21+	94 (39)	79 (31)
Other	30 (12)	24 (10)
Extramedullary disease — no. (%)		
Yes	13 (5)	25 (10)
No	230 (95)	226 (90)
Myeloma IgG — no. (%)	161 (66)	159 (63)
Previous lines of therapy — no. (%)		
1	125 (51)	125 (50)
2 or 3	88 (36)	99 (39)
≥4	30 (12)	27 (11)

Table 1. (Continued.)

Characteristics	BVd (N=243)	DVd (N=251)
Time to relapse after most recent therapy — no. (%)		
≤12 mo	49 (20)	50 (20)
>12 mo	194 (80)	201 (80)
Previous proteasome inhibitor — no. (%)		
Any	218 (90)	216 (86)
Bortezomib	210 (86)	211 (84)
Carfilzomib	31 (13)	35 (14)
Ixazomib	13 (5)	11 (4)
Previous immunomodulatory drugs — no. (%)		
Any	198 (81)	216 (86)
Lenalidomide	127 (52)	130 (52)
Thalidomide	121 (50)	144 (57)
Pomalidomide	25 (10)	19 (8)
Previous daratumumab treatment — no. (%)	3 (1)	4 (2)
Previous ASCT — no. (%)	164 (67)	173 (69)
Previous chemotherapy — no. (%)	198 (81)	206 (82)
Previous glucocorticoids — no. (%)	241 (>99)	247 (98)

* Percentages may not total 100 because of rounding. ASCT denotes autologous stem-cell transplantation, BVd belantamab mafodotin, bortezomib, and dexamethasone, DVd daratumumab, bortezomib, and dexamethasone, and R-ISS Revised International Staging System.
† Race was reported by the investigators.
‡ The Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.
§ Standard cytogenetic risk was defined by negative results for all high-risk abnormalities: t(4;14), t(14;16), and del(17p13). High cytogenetic risk was defined by the presence of at least one high-risk abnormality. High-risk abnormalities were assessed by means of interphase fluorescence in situ hybridization with the following central laboratory thresholds: 2% for t(4;14), 2% for t(14;16), and 5% for del(17p13). Local laboratory thresholds were based on local standards. Details are provided in the Supplementary Appendix.

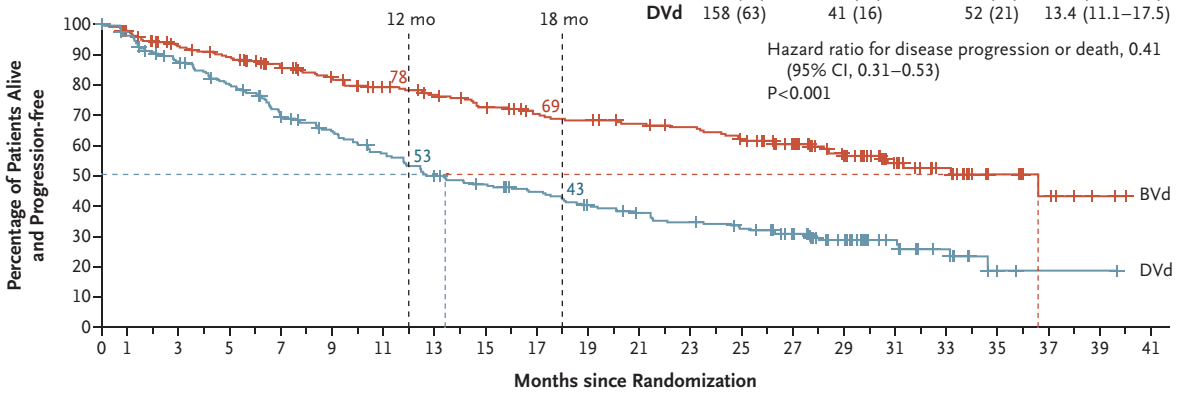
the first occurrence of worsening. In the remaining 2% of the patients who had a decrease to 20/50 in both eyes, the BCVA did not improve, treatment was discontinued, and no further examinations were performed to assess for resolution. In a post hoc analysis, the BCVA returned to the baseline level (20/25 or better in at least one eye) after the first occurrence of worsening in 94% of the patients who had a decrease to 20/50 in both eyes and in 80% of those who had a decrease to 20/200 in both eyes. The median time to resolution after the first occurrence was 9 weeks among patients with a decrease to 20/50 and 12 weeks among those with a decrease to 20/200.

Modifications of the belantamab mafodotin dose were based on the overall KVA grade. KVA events occurred in 84% of the patients; 7% had grade 2 events, and 74% had grade 3 or higher events (Table S15). For the first occurrence of a grade 2 or higher KVA event, the median time to onset was 58.0 days, and the median duration was 106.0 days. At the time of the data cutoff, the first occurrence of a KVA event had resolved, whether before or after the end of treatment exposure, in 85% of the patients. Ocular events led to reductions, delays, and discontinuations of the belantamab mafodotin dose in 44%, 78%, and 9% of the patients in the BVd group, respectively. Although more ocular events occurred in the BVd group than in the DVd group, there was no substantial difference between the treatment groups in the overall patient-reported quality of life over time (Fig. S8).

The median relative dose intensity of belantamab mafodotin was 51% for the full duration of treatment. In a post hoc analysis, the value

A Kaplan–Meier Analysis of Progression-free Survival

	Patients with an Event	Patients with Censored Data, Follow-up Ended	Patients with Censored Data, Follow-up Ongoing	Median Progression-free Survival (95% CI)
		no. (%)		*mo*
BVd	91 (37)	44 (18)	108 (44)	36.6 (28.4–NR)
DVd	158 (63)	41 (16)	52 (21)	13.4 (11.1–17.5)



No. at Risk (no. of events)																						
BVd	243	230	211	200	183	171	158	150	140	131	127	122	118	110	94	72	41	25	11	6	2	0
	(0)	(6)	(17)	(25)	(32)	(39)	(46)	(51)	(59)	(63)	(67)	(69)	(71)	(78)	(81)	(86)	(88)	(89)	(90)	(91)	(91)	(91)
DVd	251	230	205	183	155	141	124	107	99	91	80	73	67	61	52	33	19	11	2	1	1	0
	(0)	(9)	(29)	(47)	(71)	(81)	(97)	(113)	(119)	(124)	(133)	(138)	(144)	(148)	(151)	(154)	(154)	(156)	(158)	(158)	(158)	(158)

B Post Hoc Supplementary Analyses of Progression-free Survival

Analysis	BVd (N=243)	DVd (N=251)
	no. of patients with event (%)	
Disease progression or death	100 (41)	173 (69)
Disease progression	67 (28)	139 (55)
Disease progression after extended loss to follow-up	1 (<1)	6 (2)
Disease progression after the start of new antimyeloma therapy	0	0
Death	24 (10)	19 (8)
Death after extended loss to follow-up	4 (2)	2 (<1)
Death after the start of new antimyeloma therapy	4 (2)	7 (3)
Censored, follow-up ended	35 (14)	26 (10)
Censored, follow-up ongoing	108 (44)	52 (21)
Hazard ratio (95% CI)	0.41 (0.32–0.53)	

Figure 1. Progression-free Survival.

Panel A shows the Kaplan–Meier analysis of independent review committee–assessed progression-free survival in the intention-to-treat population. Panel B shows a post hoc supplementary analysis of progression-free survival in the intention-to-treat population in which any occurrence of disease progression or death after the start of a new antimyeloma therapy or after extended loss to follow-up was considered to be an event. Patients had censored data with follow-up ended if they had not had an event and had been withdrawn from the trial or if they had started a new antimyeloma therapy and therefore had missing outcome data; no further data collection is expected. Patients had censored data with follow-up ongoing if they had not been withdrawn from the trial, had not started a new antimyeloma therapy, and continued to be followed for the outcome. Two patients in the intention-to-treat population underwent randomization but were not treated and underwent repeat screening and randomization; they are counted as four unique patients. Hazard ratios were estimated with a Cox proportional-hazards model stratified according to the number of previous lines of therapy (one vs. two or three vs. four or more), previous exposure to bortezomib (yes vs. no), and the Revised International Staging System stage at screening (I vs. II or III), with treatment as a covariate. Confidence intervals were estimated with the Brookmeyer–Crowley method. The confidence intervals have not been adjusted for multiplicity and cannot be used in place of hypothesis testing. The P value was estimated with a one-sided stratified log-rank test; a two-sided P value is reported. BVd denotes belantamab mafodotin, bortezomib, and dexamethasone, DVd daratumumab, bortezomib, and dexamethasone, and NR not reached.

was 77% in the first 6 months, 68% after 6 months to 12 months, and 28% after 12 months. The median relative dose intensity of daratumumab was 95% or higher during each dosing period (i.e., cycles 1 through 3, cycles 4 through 8, and cycle 9 onward through treatment discontinuation) (Table S16). The median dose intensities of bortezomib and dexamethasone were similar in the two treatment groups (≥75% in the first eight cycles).

DISCUSSION

The interim analysis of the DREAMM-7 trial showed that, as compared with DVd therapy, BVd therapy conferred a significant benefit with respect to progression-free survival among patients who had relapsed or refractory multiple myeloma after at least one line of therapy. The hazard ratio for disease progression or death was 0.41 (95% CI, 0.31 to 0.53; P<0.001). BVd therapy was associated with a greater depth and durability of response than DVd therapy; the percentages of patients who had a stringent complete response, a complete response, and MRD-negative status were higher and the response duration was longer in the BVd group than in the DVd group. Grade 3 or higher adverse events occurred in 95% of the patients in the BVd group, and serious adverse events occurred in half. Approximately

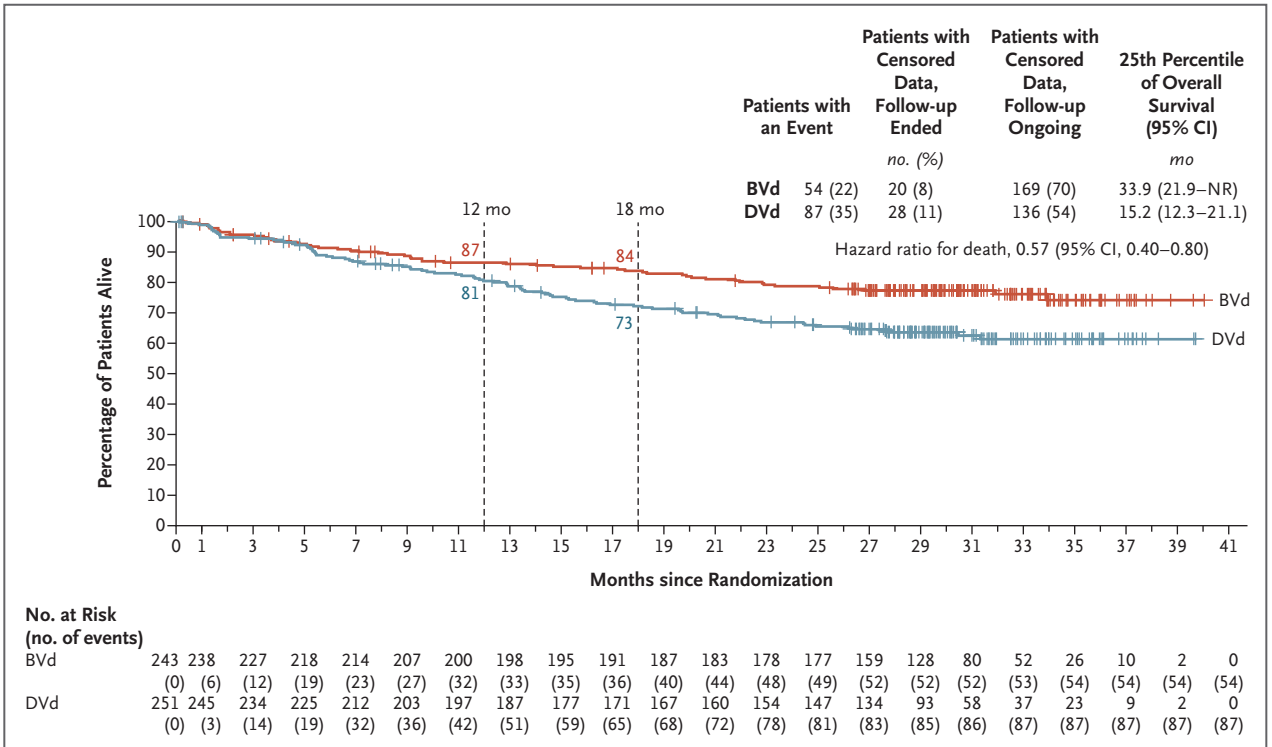


Figure 2. Overall Survival.

At the time of the data cutoff, data regarding overall survival were 29% mature. The hazard ratio for death did not meet the significance criterion; follow-up for overall survival is ongoing. Patients had censored data with follow-up ended if they had not had an event and had been withdrawn from the trial or if they had started a new antimyeloma therapy and therefore had missing outcome data; no further data collection is expected. Patients had censored data with follow-up ongoing if they had not been withdrawn from the trial, had not started a new antimyeloma therapy, and continued to be followed for the outcome. Two patients in the intention-to-treat population underwent randomization but were not treated and underwent repeat screening and randomization; they are counted as four unique patients. Hazard ratios were estimated with a Cox proportional-hazards model stratified according to the number of previous lines of therapy (one vs. two or three vs. four or more), previous exposure to bortezomib (yes vs. no), and the Revised International Staging System stage at screening (I vs. II or III), with treatment as a covariate. Confidence intervals were estimated with the Brookmeyer–Crowley method. The confidence intervals have not been adjusted for multiplicity and cannot be used in place of hypothesis testing.

Table 2. Treatment Response and Minimal Residual Disease (Intention-to-Treat Population).*

Response	BVd (N=243)	DVd (N=251)
Best overall response — no. (%)		
Stringent complete response	34 (14)	13 (5)
Complete response	50 (21)	30 (12)
Very good partial response	76 (31)	73 (29)
Partial response	41 (17)	63 (25)
Minimal response	8 (3)	11 (4)
Stable disease	25 (10)	36 (14)
Progressive disease	4 (2)	12 (5)
Not evaluable	5 (2)	13 (5)
Complete response or better		
No. of patients	84	42
% (95% CI)	35 (29–41)	17 (13–22)
Very good partial response or better		
No. of patients	160	116
% (95% CI)	66 (60–72)	46 (40–53)
Any response: partial response or better		
No. of patients	201	179
% (95% CI)	83 (77–87)	71 (65–77)
Clinical benefit: minimal response or better		
No. of patients	209	190
% (95% CI)	86 (81–90)	76 (70–81)
Median response duration (95% CI) — mo†	35.6 (30.5–NR)	17.8 (13.8–23.6)
25th Percentile of response duration (95% CI) — mo†	18.8 (13.2–23.5)	9.0 (6.4–10.4)
Median time to first response (range) — mo‡	1.4 (0.7–8.4)	0.85 (0.7–11.1)
Median time to best response (range) — mo§	4.5 (0.7–32.5)	2.2 (0.7–25.7)
MRD-negative status¶		
Patients with complete response or better		
No. of patients	60	24
% (95% CI)	25 (19–31)	10 (6–14)
Patients with very good partial response or better		
No. of patients	94	43
% (95% CI)	39 (33–45)	17 (13–22)
MRD-negative status sustained for ≥12 mo¶		
Patients with complete response or better		
No. of patients	24	6
% (95% CI)	10 (6–14)	2 (1–5)

* The confidence intervals have not been adjusted for multiplicity and cannot be used in place of hypothesis testing. Two patients in the intention-to-treat population underwent randomization but were not treated and underwent repeat screening and randomization; they are counted as four unique patients. MRD denotes minimal residual disease, and NR not reached.

† Duration of response is defined as the time from the first documented evidence of a partial response or better to the occurrence of disease progression or death from any cause.

‡ Time to first response is defined as the time from the date of randomization to the first documented evidence of a partial response or better among patients who had a confirmed partial response or better.

§ Time to best response is defined as the time from the date of randomization to the earliest date of achieving the best response among patients who had a confirmed partial response or better.

¶ MRD-negative status was assessed by means of next-generation sequencing at a sensitivity of 10^{-5} or lower.

Table 3. Adverse Events Reported in at Least 15% of Patients in Either Group (Safety Population).*

Event	BVd (N=242)		DVd (N=246)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	no. of patients (%)			
Any adverse event	242 (100)	230 (95)	246 (100)	192 (78)
Blood and lymphatic system disorders				
Any	185 (76)	151 (62)	158 (64)	109 (44)
Thrombocytopenia†	167 (69)	134 (55)	122 (50)	87 (35)
Anemia‡	46 (19)	20 (8)	65 (26)	25 (10)
Infections and infestations				
Any	170 (70)	75 (31)	166 (67)	49 (20)
Pneumonia	44 (18)	28 (12)	22 (9)	10 (4)
Coronavirus disease 2019	58 (24)	14 (6)	49 (20)	11 (4)
Upper respiratory tract infection	48 (20)	0	49 (20)	0
Ocular events				
Any	191 (79)	82 (34)	72 (29)	7 (3)
Blurred vision	160 (66)	53 (22)	26 (11)	2 (1)
Dry eye	123 (51)	17 (7)	17 (7)	0
Photophobia	114 (47)	5 (2)	6 (2)	0
Eye irritation	103 (43)	12 (5)	13 (5)	0
Foreign-body sensation in eye	106 (44)	8 (3)	10 (4)	0
Eye pain	77 (32)	2 (1)	8 (3)	1 (<1)
Cataract	49 (20)	17 (7)	25 (10)	6 (2)
Other				
Diarrhea	78 (32)	9 (4)	77 (31)	10 (4)
Peripheral sensory neuropathy	61 (25)	2 (1)	51 (21)	1 (<1)
Peripheral neuropathy	50 (21)	3 (1)	55 (22)	10 (4)
Constipation	46 (19)	2 (1)	56 (23)	1 (<1)
Fatigue	47 (19)	9 (4)	48 (20)	6 (2)
Increased alanine aminotransferase level	47 (19)	14 (6)	29 (12)	3 (1)
Pyrexia	45 (19)	1 (<1)	25 (10)	3 (1)
Nausea	39 (16)	2 (1)	30 (12)	0
Insomnia	38 (16)	3 (1)	47 (19)	2 (1)
Increased aspartate aminotransferase level	37 (15)	3 (1)	13 (5)	0
Increased γ-glutamyltransferase level	36 (15)	22 (9)	11 (4)	4 (2)
Back pain	22 (9)	3 (1)	36 (15)	5 (2)
Infusion-related reaction§	8 (3)	1 (<1)	42 (17)	4 (2)

* Adverse events were graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

† If platelet-count decrease is also included, the percentage of patients with a thrombocytopenia event of any grade is 87% with BVd and 65% with DVd, and the percentage of patients with a grade 3 or higher thrombocytopenia event is 73% and 46%, respectively.

‡ Decreased red-cell count was not reported.

§ Infusion-related reactions are based on a hybrid of terms identified in the electronic case report form and a list of terms identified by GSK internal review. The event had to start within 24 hours after the infusion and lead to dose interruption or delay or to discontinuation of the trial drug.

Table 4. Worsening of BCVA in Both Eyes among Patients in the BVd Group with Normal BCVA at Baseline.*

Measure	Worsening to 20/50	Worsening to 20/200
No. of patients with event/total no. (%)	82/242 (34)	5/242 (2)
First event		
Median time from start of treatment to onset of first event (range) — days	73.5 (16–753)	105 (47–304)
Improvement after first event — no./total no. (%)	80/82 (98)	5/5 (100)
Median time from onset of first event to improvement (range) — days	22 (6–257)	19 (8–26)
Resolution after first event — no./total no. (%)	77/82 (94)	4/5 (80)
Median time from onset of first event to resolution (range) — days	64 (8–908)	87 (22–194)
Last event		
Improvement after last event — no./total no. (%)	75/82 (91)	3/5 (60)
Median time from onset of last event to improvement (range) — days	22 (8–173)	19 (8–26)

* Normal best corrected visual acuity (BCVA) was defined as 20/25 or better in at least one eye. Improvement was defined as a BCVA of better than 20/50 or 20/200 (depending on the level of worsening) in both eyes. Resolution was defined as a return to the baseline BCVA.

one quarter of the patients in the BVd group discontinued any of the three drugs in BVd because of treatment-related toxic effects.

The median progression-free survival of 13.4 months (95% CI, 11.1 to 17.5) in the DVd group is consistent with that seen in the CASTOR trial (16.7 months; 95% CI, 13.1 to 19.4) and better than the outcome among patients with multiple myeloma in a nontrial setting (8.3 months).[17-19] Although cross-trial comparisons should be interpreted with caution, the median progression-free survival of 36.6 months (95% CI, 28.4 to NR) in the BVd group is similar to, or better than, that reported in other trials of triplet combination regimens that included anti-CD38 monoclonal antibodies and proteasome inhibitors and were used in similar populations; the median progression-free survival was 28.6 months in the CANDOR trial and 35.7 months in the IKEMA trial.[20,21] In the CARTITUDE-4 trial, patients who had disease that was refractory to lenalidomide after at least one line of therapy were treated with ciltacabtagene autoleucel, a BCMA-targeting chimeric antigen receptor (CAR) T-cell therapy. Progression-free survival at 12 months was 76%, and the corresponding estimate in the DREAMM-7 trial was 78%.[22]

The broad clinical benefit observed with BVd supports its potential integration into current treatment strategies used at the time of the first relapse or later. The PERSEUS trial recently showed a benefit of frontline treatment with daratumumab, bortezomib, lenalidomide, and dexamethasone.[23] Once this frontline regimen is adopted, disease may become refractory to maintenance therapy with daratumumab and lenalidomide after frontline treatment, and new second-line regimens may be needed. The DREAMM-7 trial included a small number of patients who had had exposure to daratumumab, and patients with disease that was refractory to anti-CD38 antibody therapies were excluded from the trial; however, BVd may offer patients an alternative to retreatment with an anti-CD38 antibody. Furthermore, the presence of soluble BCMA at the time of disease progression may indicate retained BCMA expression in tumor cells after treatment with belantamab mafodotin. Therefore, it is anticipated that patients may derive benefit from other BCMA-targeted retreatment after progression.[16,24,25] However, this result does not rule out the presence of mutations in the tumor necrosis factor receptor superfamily member 17 gene, which encodes BCMA; further studies would be needed to confirm that soluble BCMA is a surrogate for sensitivity to subsequent BCMA-targeting agents.

Adverse events associated with the use of BVd were consistent with those described previously with belantamab mafodotin.[9,10] The overall incidence of adverse events was high because the analysis included adverse events associated with

all drugs in the triplet combination regimen; the incidence may also reflect the treatment duration. In addition, enrollment occurred during the Covid-19 pandemic, which may have led to a higher level of treatment discontinuation than that reported in previous studies. Ocular side effects, which are a known risk with belantamab mafodotin, were managed with dose modifications, including delays and reductions. The efficacy of BVd was maintained even with delays and reductions of the belantamab mafodotin dose, which resulted in the lower relative dose intensity reported for belantamab mafodotin. Most patients who had a decrease in the BCVA subsequently had improvement or had their vision return to the baseline level. Resolution could not be confirmed in all patients because of progressive disease, death, or loss to follow-up. Some patients had multiple occurrences of a decrease in the BCVA, but the likelihood of resolution after the first occurrence was similar to that after the last occurrence among patients with more than one occurrence of worsening. Ocular adverse events occurred in 79% of the patients in the BVd group and 29% of those in the DVd group, findings that suggest a background incidence of such events in the general population of patients with multiple myeloma and that may reflect the intense ocular monitoring mandated by the use of belantamab mafodotin. Despite the higher incidence of ocular adverse events in the BVd group, overall patient-reported health-related quality of life did not differ substantially between the treatment groups over time.

The use of BCMA-targeting bispecific T-cell engager (BITE) or CAR T-cell therapies requires more intensive monitoring and is associated with life-threatening toxic effects, including cytokine release syndrome and immune effector cell–associated neurotoxicity syndrome. Belantamab mafodotin administered as a short outpatient infusion offers a less burdensome treatment option for patients and does not require monitoring for life-threatening toxic effects. The incidence of infections, including opportunistic infections — a known risk with the use of BCMA-targeting BITE and CAR T-cell agents[26-29] — was low and similar in the two treatment groups in this trial.

Limitations of this trial included limited racial diversity. There was the potential for bias from the open-label design, but such bias is unlikely because the investigators and the independent review committee were largely in agreement in their assessment of progressive disease. There was reporting bias of ocular events toward the BVd group because of the higher frequency of ocular examinations.

As compared with DVd, BVd conferred a significant benefit with respect to progression-free survival among patients with relapsed or refractory multiple myeloma after at least one line of therapy. In addition, BVd was associated with serious adverse events in 50% of patients. However, the strong results for progression-free survival and the deep and durable response with BVd support the potential for BVd to become a therapeutic option for patients with multiple myeloma at or after the first relapse.

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APPENDIX

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