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Exposure-response and dose simulation of belantamab mafodotin in combination with standards of care in patients with relapsed/refractory multiple myeloma

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Running head: E-R and dose simulation of belamaf regimens

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Author contributions

SL, **PGR**, **PM, MVM**, and **MAD** contributed to study conception or design and data interpretation. **GF-B** and **FC** contributed to study conception or design, data acquisition, data analysis, and data

interpretation. **TP** contributed to data acquisition, data analysis, and data interpretation. **YLH** contributed to data analysis and data interpretation. **AM** and **SR-G** contributed to data acquisition and data interpretation. **KB**, **MM**, and **HAA**, contributed to data interpretation.

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Abstract

Belantamab mafodotin is approved globally for relapsed/refractory multiple myeloma (RRMM) based on the phase 3 DREAMM-7 (belantamab mafodotin, bortezomib, dexamethasone [BVd]) and DREAMM-8 (belantamab mafodotin, pomalidomide, dexamethasone) studies. Ocular events in these studies were common, transient, and associated with high rates of resolution. Exposure-response analyses using Cycle 1 exposures (data from the DREAMM-6, DREAMM-7, and DREAMM-8 trials) and BVd dosing regimen simulation (using a previously-developed and validated framework) were performed to support benefit-risk analysis of belantamab mafodotin dosing strategies to improve outcomes. Higher Cycle 1 belantamab mafodotin exposure was significantly associated with higher probabilities of overall response, very good partial response or better (≥VGPR), and shorter time to response, as well as ocular events including grade ≥2/≥3 ophthalmic exam findings (OEFs), and best-corrected visual acuity worsening to 20/50 or worse in both eyes. However, multivariate models predicted that the benefit of increased probability of ≥VGPR with a 2.5 mg/kg vs 1.9 mg/kg starting dose (70.4% vs 54.3%) outweighed the risk for modest increases in clinically meaningful ocular events. Simulated regimens with a 2.5 mg/kg first dose demonstrated high efficacy, with regimens that stepped down to 1.9 mg/kg and utilized schedule extensions (planned or in response to ocular events) showing improved tolerability. Altogether, a belantamab mafodotin starting dose of 2.5 mg/kg in RRMM is important to achieve deeper response and outweighs modest improvements in tolerability from a 1.9 mg/kg starting dose. Subsequent step-down to 1.9 mg/kg along with schedule extensions can be used to manage tolerability while still achieving meaningful efficacy.

Keywords: Belantamab mafodotin; multiple myeloma; exposure-response; simulation; dose

Introduction

B-cell maturation antigen (BCMA)-targeting therapies have demonstrated transformational survival benefits for patients with relapsed/refractory multiple myeloma (RRMM), improving the therapeutic landscape.[1-3] Belantamab mafodotin is a unique BCMA-targeting therapy as an antibody-drug conjugate (ADC).[4] It has a multimodal mechanism of action consisting of cytotoxic payload- and immune-mediated effects that may contribute to an adaptive immune response.[5] Belantamab mafodotin has been evaluated for the treatment of RRMM as monotherapy[6-8] and in combination regimens with lenalidomide and dexamethasone (BRd as part of the DREAMM-6 study), bortezomib and dexamethasone (BVd as part of the DREAMM-6 and DREAMM-7 studies), and pomalidomide and dexamethasone (BPd; DREAMM-8 study).[9-12] Based on robust efficacy observed in the DREAMM-7 and DREAMM-8 studies, BVd and BPd have been approved in several countries, including the United States (BVd only to date) and European Union (both BVd and BPd).[13] Similar to other ADCs, ocular events commonly occur during belantamab mafodotin treatment,[14-16] and are transient with high rates of resolution.[9,10,17] Clinical trials of belantamab mafodotin used the Keratopathy and Visual Acuity (KVA) scale[18] to determine event grades and dose modification strategies to manage ophthalmic exam findings (OEFs; i.e, changes to best-corrected visual acuity and slit-lamp exam findings) and in turn minimize the impact of any ocular events.

An analysis of DREAMM-7 and DREAMM-8 found that most patients treated with BVd or BPd had dose delays resulting in extended dosing intervals, with responses being achieved, maintained, or deepened during these extended times between doses.[19] Therefore, additional analyses were of interest to further explore the effects of dosing schedule on treatment outcomes. Exposure-response analyses are valuable to understand the benefit-risk profiles of therapies, and simulations of different dosing strategies with integration of longitudinal efficacy and safety models can be particularly useful for agents like belantamab mafodotin, for which dose modifications are often used to manage tolerability.[19,20] A simulation framework integrating pharmacokinetics (PK), a pharmacodynamic (PD) measure of efficacy (M-protein), and ocular safety (OEFs) was developed. With this framework, simulations of BVd and BPd outcomes using DREAMM-7 and DREAMM-8 dosing strategies yielded similar outcomes to those demonstrated in the trials, supporting use of the framework to simulate alternative belantamab mafodotin dosing strategies.[21]

Here, we report an exposure-response analysis of the DREAMM-6, DREAMM-7, and DREAMM-8 studies, and results from simulations of various belantamab mafodotin dosing strategies for BVd.

Methods

Exposure-response

Studies

The exposure-response analysis included data from studies evaluating belantamab mafodotin combinations in patients who received ≥1 prior therapy line: the phase 1/2 DREAMM-6 study, which evaluated BRd and BVd at doses including 1.9 mg/kg or 2.5 mg/kg (3.4 mg/kg was not included in the exposure-response analysis) at various schedules (**Supplementary Table 1**); the phase 3 DREAMM-7 study, which evaluated BVd at 2.5 mg/kg every 3 weeks (Q3W); and the phase 3 DREAMM-8 study, which evaluated BPd at 2.5 mg/kg in Cycle 1 followed by 1.9 mg/kg Q4W onward.

Patients who received BRd, BVd, or BPd in these studies were included in exposure-safety analyses if they received at least one dose of belantamab mafodotin and had at least one measurable PK sample available. Patients included in exposure-efficacy analyses must have also had measurable disease at baseline.

Ethics approval and consent to participate

Studies included in these analyses were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent before enrollment, and the trial protocols and amendments were approved by the appropriate ethics body at each participating institution.

Exposure measures and exposure-response endpoints

Individual Cycle 1 exposures for belantamab mafodotin and its free payload (cysteine maleimidocaproyl monomethyl auristatin F [cys-mcMMAF]) were derived using a population PK model[22] with actual patient dosing, demographics, disease characteristics, and PK post-hoc parameters that were generated from individual PK data.

Exposure-response relationships assessed for efficacy included probabilities of overall response, very good partial response or better (≥VGPR), complete response or better (≥CR), minimal residual disease negativity (MRD-), progression-free survival (PFS), overall survival (OS), duration of response, and time to response. For safety, several assessments were performed, the most clinically relevant of which were probability of and time to first grade ≥2 and ≥3 ocular adverse event (oAE) per Common Terminology Criteria for Adverse Events (CTCAE), worsening of BCVA to 20/50 or worse in both eyes, and grade ≥2 and ≥3 OEFs per the KVA scale.

Covariate assessments were also performed to determine potential impacts on exposure-response endpoints (detailed in **Supplementary Methods**).

Statistical analysis

Logistic regression models were used to determine probability of efficacy/safety events based on exposure, Kaplan–Meier plots were generated for time-to-event endpoints (stratified by exposure quartiles), and Cox proportional hazards (CPH) models were used to determine exposure-response relationships for time-to-event endpoints. Reported odds ratios and hazard ratios (HRs) are for comparison of rates (odds or hazards) in dose/exposure between a 1.9 mg/kg and 2.5 mg/kg belantamab mafodotin starting dose.

Integrated exposure-efficacy and exposure-safety analysis

Plots integrating exposure-response curves for probability of ≥VGPR and safety endpoints were generated for visual benefit-risk assessment. Multivariate model predictions incorporating baseline characteristics and disease-related covariates were performed to determine the benefit-risk profile of a 2.5 mg/kg starting dose compared to a 1.9 mg/kg starting dose of belantamab mafodotin.

Simulations

Creation and verification of the simulation framework has been previously published.[21] Briefly, a tumor growth inhibition model was developed to model changes in serum M-protein concentrations over time, and a continuous-time Markov model was developed to model changes in OEF grades per the KVA scale; individual belantamab mafodotin concentrations included in both models were derived from the population PK model.[22]

The final M-protein, KVA, and PK models were integrated to form a framework capable of simulating efficacy and safety outcomes for various belantamab mafodotin dosing regimens, while accounting for dropouts due to progressive disease and other reasons (i.e., adverse events or loss of follow-up). For each simulated regimen, dose modifications (dose holds and re-initiation, reductions, schedule changes) were informed by predicted KVA grade. Here, the framework was used to simulate the following dosing regimens for belantamab mafodotin in the BVd combination: DREAMM-7 reference regimen (2.5 mg/kg Q3W with dose reduction to 1.9 mg/kg Q3W after grade ≥2 OEF); Food and Drug Administration (FDA)-approved regimen (2.5 mg/kg Q3W with dose reduction to 1.9 mg/kg Q3W after grade ≥2 OEF, and schedule extension to 1.9 mg/kg Q8W for the second grade ≥2 OEF); 1 planned step-down (2.5 mg/kg for 1 dose, then 4 weeks later 1.9 mg/kg Q4W, with dose reduction to 1.9 mg/kg Q8W after grade ≥2 OEF); and 2 planned step-downs (2.5 mg/kg for one dose, then eight weeks later 1.9 mg/kg Q8W, then 1.9 mg/kg Q12W at Cycle 7, with schedule extension to 1.9 mg/kg Q12W after grade ≥2 OEF).

Results

Patients

The exposure-efficacy and safety analyses included 516 patients (**Tables 1 and 2**). The median age was 66.0 (range 32.0, 86.0) years, 60.3% of patients were male, approximately 70.0% of patients had IgG type myeloma, and median baseline soluble BCMA (sBCMA) level was approximately 40.0 ng/mL.

Exposure-efficacy analysis

Comparing 2.5 mg/kg and 1.9 mg/kg doses/exposures, Cycle 1 belantamab mafodotin average concentration over 21 days (C_{avg21}) was significantly associated with the probability of overall response (odds ratio 1.91 [95% confidence interval [CI] 1.49-2.47]) and ≥VGPR (odds ratio 2.09 [95% CI 1.68-2.64]), where higher exposure led to increased probability of each, and time to response (HR 1.28 [95% CI 1.14-1.43]), where higher exposure led to earlier response. While ≥CR, MRD-, time to best response, PFS, and OS models included a significant exposure metric in univariate analyses, no exposure metrics were retained in the final models (**Supplementary Table 2**). Results from covariate analyses are also reported in **Supplementary Table 2**.

Exposure-safety analysis

Higher Cycle 1 belantamab mafodotin C_{avg21} was significantly associated with increased probability of grade ≥2 OEFs (odds ratio 2.38 [95% CI 1.73-3.35]), grade ≥3 OEFs (odds ratio 1.60 [95% CI 1.26-2.04]), and BCVA worsening to 20/50 or worse in both eyes (odds ratio 1.32 [95% CI 1.10-1.60]). Exposure was not associated with the probability of grade ≥2 or ≥3 oAEs (**Supplementary Table 3**). Results from covariate analyses are also reported in **Supplementary Table 3**.

Integrated exposure-response analyses

Visual comparisons of efficacy and safety exposure-response curves showed that the ≥VGPR curve had a steeper slope than the curves for grade ≥3 oAEs and BCVA worsening to 20/50 or worse in both eyes (**Figure 1**). The ≥VGPR curve had a similar slope as grade ≥3 OEFs; however, the effect of lower first-dose concentrations on probability of ≥VGPR were more pronounced than effects of higher first-dose concentrations on probability of grade ≥3 OEFs.

Multivariate model predictions indicated that a 2.5 mg/kg starting dose of belantamab mafodotin leads to higher probability of ≥VGPR than a 1.9 mg/kg starting dose (70.4% vs 54.3% probability), without meaningfully affecting rates of ocular events (grade ≥3 OEFs 78.7% vs 70.4%; grade ≥3 oAEs 52.2% vs 52.2%; BCVA worsening to 20/50 or worse in both eyes 33.3% vs 27.5%; **Table 3**).

Simulations of belantamab mafodotin dosing regimens for BVd

Outcomes were simulated over 50 months of follow-up. Simulations for each regimen used dose holds for grade ≥2 OEFs followed by dose reduction after resolution to grade ≤1; for DREAMM-7 reference simulation, dose reductions were triggered by grade ≥3 OEFs as specified in the clinical study protocol. Predicted dose holds, dose reductions, and the number of doses administered by regimen are presented in **Supplementary Tables 4** and **5**.

Simulation of the DREAMM-7 dosing regimen (2.5 mg/kg Q3W with dose reduction to 1.9 mg/kg Q3W for OEFs) predicted a ≥VGPR rate of 61.5%, 12-month PFS of 80.3%, and grade ≥3 OEFs in 85.5% (**Table 4**), which is broadly consistent with the observed results from the DREAMM-7 study.[10]

Simulation of the FDA-approved regimen (2.5 mg/kg Q3W with dose reduction to 1.9 mg/kg Q3W for grade ≥2 OEFs, followed by 1.9 mg/kg Q8W for subsequent grade ≥2 OEFs)[23] showed similar predicted

outcomes (≥VGPR rate, 60.0%; 12-month PFS, 80.0%; grade ≥3 OEFs, 75.5%). Simulated regimens utilizing 2.5 mg/kg for one dose followed by a planned step-down (similar to the regimen used in DREAMM-8) had acceptable predicted benefit-risk profiles, with improvements in safety but reduced efficacy compared to the DREAMM-7 and FDA-approved regimens (1 planned step-down to 1.9 mg/kg Q4W: ≥VGPR rate 57.0%, 12-month PFS 77.3%, grade ≥3 OEFs in 66.5%; 2 planned step-downs to 1.9 mg/kg Q8W, then 1.9 mg/kg Q12W at Cycle 7: ≥VGPR rate 46.0%, 12-month PFS 68.6%, grade ≥3 OEFs in 48.5%).

Overlaid Kaplan-Meier curves for predicted PFS of each simulated regimen showed large overlap between the DREAMM-7 dosing regimen, the FDA-approved regimen, and 1 planned step-down (**Figure 2**).

Discussion

With the recent approval of belantamab mafodotin combinations for RRMM in multiple countries and healthcare jurisdictions,[13] insights into the benefit-risk profile of the regimens are critical to inform clinical decision-making. Exposure-response analyses indicated that higher belantamab mafodotin exposure at the first dose is associated with deeper responses, higher probabilities of grade ≥3 OEFs, and BVCA worsening to 20/50 or worse in both eyes. Integrated analysis of the efficacy and safety exposure-response curves emphasized the importance of higher first-dose exposure on the probability of ≥VGPR. In line with this, multivariate model predictions indicated that a higher starting dose of belantamab mafodotin (2.5 mg/kg) had a probability of ≥VGPR that was 16% higher than that for the 1.9 mg/kg starting dose, without meaningful differences in rates of ocular events (no difference in grade ≥3 oAEs, 6% higher probability of BCVA worsening to 20/50 or worse in both eyes, and 8% higher probability of grade ≥3 OEFs with 2.5 mg/kg). The lack of an exposure-safety relationship identified for oAEs per the CTCAE scale may be related to the limitations of the CTCAE scale for ocular events; while the CTCAE scale measures signs and symptoms of ocular events, the KVA scale uses findings from the ophthalmic examination, which was used to manage ocular events for patients.[24] While the effects of baseline ocular conditions were not assessed in this exposure-response analysis, in DREAMM-7 and DREAMM-8, rates of oAEs were similar between patients with/without baseline ocular conditions (DREAMM-7: 74%/79%; DREAMM-8: 87%/91%), suggesting that with appropriate monitoring (aligning

with prescribing information[23]) there is no increased risk of oAEs in patients with ocular conditions at baseline.[25]

Simulation of outcomes with the DREAMM-7 regimen (2.5 mg/kg Q3W and dose reductions to 1.9 mg/kg Q3W after grade ≥2 OEF) were similar to those observed in the DREAMM-7 study (simulated predictions/observed data: ≥VGPR 61.5%/66.0%, 12-month PFS 80.3%/78.0%, and grade ≥3 OEFs 85.5%/74.0%).[10] Simulations of alternative belantamab mafodotin dosing regimens for BVd showed that compared to the dosing used in DREAMM-7, the FDA-approved regimen (2.5 mg/kg Q3W with dose reduction to 1.9 mg/kg Q3W after grade ≥2 OEF, and schedule extension to 1.9 mg/kg Q8W for the second grade ≥2 OEF) demonstrated similar efficacy, with modest reduction in OEFs. Regimens with an initial 2.5 mg/kg dose and 1 or 2 planned step-downs still produced acceptable efficacy and improved ocular safety. A separate analysis using this simulation framework further supported that a 2.5 mg/kg starting dose produces the highest efficacy, and schedule extensions (Q6W, Q8W) after the first BVd dose, even without planned step-down to 1.9 mg/kg, can improve tolerability while continuing to demonstrate efficacy.[21] Taken together, these analyses support that an initial 2.5 mg/kg dose with higher initial dose intensity (including more frequent early dosing), and subsequent schedule extensions can improve long-term tolerability by decreasing the probability of ocular events.

These results align with those observed in dose-evaluation studies of belantamab mafodotin in RRMM. In Arm B of the DREAMM-6 (BVd) and ALGONQUIN (BPd) trials, the 2.5 mg/kg Q3W and Q4W cohorts, respectively, had the deepest responses, with 1.9 mg/kg regimens showing improved tolerability but with a tradeoff in efficacy in RRMM.[26,27] BVd and BPd at 2.5 mg/kg starting dose regimens demonstrated high efficacy in the DREAMM-7 and DREAMM-8 studies, including an OS benefit for BVd (BPd analysis ongoing).[3,9] Most patients who received BVd or BPd in DREAMM-7/DREAMM-8 had a dose hold of belantamab mafodotin, and these patients continued to develop, maintain, or have deepening responses.[19,28] This suggests that in clinical practice, extended dosing intervals after an initial period of higher dose intensity may be frequent and necessary, but patients can still derive robust efficacy. The results from our analysis indicate that use of a 2.5 mg/kg first dose in RRMM with higher initial dose intensity induces deep responses, which can be maintained after dose modifications with schedule extension to optimally manage ocular events. For newly-diagnosed MM, dose-finding studies have shown that a lower belantamab mafodotin starting dose of 1.9 mg/kg may be adequate to achieve high efficacy,[29,30] potentially reflecting differences in disease biology between diagnosis and relapse.[31]

Prospective clinical trials in RRMM and newly-diagnosed MM are ongoing to assess the efficacy and safety of lower belantamab mafodotin starting dose intensities in various combination regimens (DREAMM-10 [BRd in newly-diagnosed MM]: 1.9 mg/kg Q8W for 24 weeks, then 1.9 mg/kg Q12W thereafter; DREAMM-15 [BVd, BPd, or belantamab mafodotin, carfilzomib, and dexamethasone in RRMM]: 2.5 mg/kg for one dose, then 8 weeks later 1.9 mg/kg Q8W for 2 cycles, and 1.9 mg/kg Q12W thereafter), which will further inform these findings.[32,33]

Our exposure-response analysis was strengthened by inclusion of data for 3 different combination regimens from two phase 3 trials and a dose-optimization study, allowing for a robust evaluation. The multiple safety endpoints evaluated also strengthen the conclusions of the analysis. The exposure-response analyses did not account for exposure of the combination partners, which is a potential limitation of the analysis. However, the simulations data were from robust models informed by several studies and verified against results from the DREAMM-7 and DREAMM-8 trials. Use of the simulation framework allowed for evaluation of large number of dosing regimens and dose modification options to improve understanding of belantamab mafodotin dosing. Of note, as efficacy models did not evaluate the contribution of different agents in the combinations separately, underprediction of efficacy for regimens with longer dosing intervals could have occurred. Additionally, results from the simulations are hypothesis-generating only, and clinical studies are required to confirm findings of the alternate dosing regimens.

In summary, exposure-response analyses in RRMM indicated that higher belantamab mafodotin exposure with the first dose is associated with deeper responses (≥VGPR), which is critical for improved long-term, durable clinical outcomes such as PFS and OS.[34] Importantly, lowering the starting dose from 2.5 mg/kg to 1.9 mg/kg was associated with meaningful reductions in efficacy without substantial improvements in ocular safety. Simulations of BVd dosing scenarios demonstrated the potential for high efficacy with a 2.5 mg/kg starting dose, and subsequent step down and schedule extensions after the initial high dose intensity (as used in the DREAMM-8 study [2.5 mg/kg for 1 dose, then step-down to 1.9 mg/kg Q4W and schedule extension to Q8W after grade ≥2 OEF] and the ongoing DREAMM-15 study [2.5 mg/kg Q8W for 1 dose, then step-down to 1.9 mg/kg Q8W for 2 cycles followed by a 1.9 mg/kg Q12W maintenance])[9,32] can improve tolerability while still providing meaningful efficacy. Taken together, a 2.5 mg/kg starting dose of belantamab mafodotin with higher dose intensity is important to achieve higher efficacy, with subsequent schedule extensions improving tolerability while still

maintaining response. This strategy led to robust positive efficacy outcomes versus standards of care (including daratumumab, bortezomib and dexamethasone in DREAMM-7 and pomalidomide, bortezomib, and dexamethasone in DREAMM-8), and provides a foundation for future studies to further improve patient outcomes.[3,9,19,35,36]

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Table 1. Summary of efficacy and safety covariates related to baseline demographics, prior therapy, and disease status

	N=516
Age, median (range), years	66.0 (32.0-86.0)
Male, n (%)	311 (60.3)
Race, n (%)	
White	444 (86.0)
Black or African American	17 (3.3)
Asian	51 (9.9)
North East Asian	43 (8.3)
European country, n (%)	266 (51.6)
Baseline body weight, median (range), kg	76.0 (41.0-170)
Baseline BMI, median (range), kg/m^2	26.9 (14.0-47.5)
ECOG performance status, n (%)	
0	257 (49.8)
1	236 (45.7)
2	23 (4.5)
International Staging System stage at screening, n (%)	
I	258 (50.0)
II	206 (39.9)
III	52 (10.1)
Extramedullary disease, n (%)	54 (10.5)
High cytogenetic risk, n (%)	149 (28.9)
Refractory to both immunomodulatory drugs and proteasome inhibitors, n (%)	48 (9.3)
Prior lines of therapy, n (%)	
1	231 (44.8)
2–3	176 (34.1)
≥4	109 (21.1)
Prior anti-CD38 treatment, n (%)*	102 (19.8)
DREAMM-6	63 (50.8)
DREAMM-7	3 (1.2)
DREAMM-8	36 (24.0)
Prior bortezomib treatment, n (%)	453 (87.8)

*DREAMM-7 excluded patients who were intolerant to daratumumab or refractory to any anti-CD38 therapy (defined as progressive disease during treatment with anti-CD38 therapy, or within 60 days of completing that treatment).

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group

Table 2. Summary of efficacy and safety covariates related to baseline laboratory findings, organ function, ocular characteristics, and belantamab mafodotin dosing

	N=516
Baseline sBCMA level, median (range), ng/mL	40.1 (0.975-1190)
Baseline Beta-2 microglobulin level, median (range), nmol/L	254 (94.9-1530)
Baseline lactate dehydrogenase, median (range), U/L	191 (59.0-3020)
Baseline albumin, median (range), g/L	41.0 (21.0-52.0)
Baseline IgG level, median (range), g/L	14.8 (0.650-96.3)
IgG type myeloma, n (%)	362 (70.2)
Renal function, n (%)	
Normal	183 (35.5)
Mild impairment	223 (43.2)
Moderate/severe impairment	110 (21.3)
Hepatic function, n (%)	
Normal	458 (88.8)
Mild/moderate/severe impairment	58 (11.2)
History of dry eye, n (%)	74 (14.3)
Keratopathy presence, n (%)	
Mild	104 (20.2)
Severe	4 (0.8)
Baseline BCVA best eye, median (range), logMAR	0 (-0.204, 2.00)
Baseline BCVA worst eye, median (range), logMAR	0 (-0.204, 1000)
Baseline platelet count, median (range), 10^9/L	177 (35.0-620)
Belantamab mafodotin schedule, n (%)	
Single dose, Q3W or Q4W	292 (56.6)
Split dose, 50:50 on Day 1 and Day 8 Q3W	26 (5.0)
Single dose, Q6W or Q8W	36 (7.0)
Single dose, Q6W with dose step-down after Cycle 1	12 (2.3)
Single dose, Q4W with dose step-down after Cycle 1	150 (29.1)

BCVA, best-corrected visual acuity; IgG, immunoglobulin G; QxW, every x weeks; sBCMA, soluble baseline B-cell maturation antigen

Table 3. Multivariate model predictions for belantamab mafodotin starting doses

Probability, % (95% CI)	**1.9 mg/kg**	**2.5 mg/kg**
≥VGPR	54.3 (46.4-61.9)	70.4 (65.3-75.0)
Grade ≥3 OEFs (KVA scale)	70.4 (62.9-76.8)	78.7 (74.5-82.3)
Grade ≥3 oAEs (CTCAE scale)	52.2 (45.8-58.6)	52.2 (45.8-58.6)
BCVA worsening to 20/50 or worse in both eyes	27.5 (21.9-34.0)	33.3 (29.0-37.9)

BCVA, best-corrected visual acuity; CTCAE, Common Terminology Criteria for Adverse Events; KVA, Keratopathy and Visual Acuity; oAE, ocular adverse event; OEF, ophthalmic examination finding; VGPR, very good partial response

Table 4. Simulation of BVd dosing regimens

Belantamab mafodotin dosing regimen for BVd*	**ORR, % (95% PI)**	**≥VGPR, % (95% PI)**	**12-month PFS, % (95% PI)**	**Grade ≥3 OEFs, % (95% PI)**
Reference (DREAMM-7): • 2.5 mg/kg Q3W • Restart at 1.9 mg/kg Q3W after OEF resolution†	91.0 (88.0-93.5)	61.5 (57.0-65.0)	80.3 (76.2-84.0)	85.5 (81.5-89.5)
FDA-approved regimen: • 2.5 mg/kg Q3W • Restart at 1.9 mg/kg Q3W after OEF resolution (1.9 mg/kg Q8W for subsequent events)	91.5 (88.5-93.5)	60.0 (55.5-64.5)	80.0 (76-83.7)	75.5 (70.5-80)
1 planned step-down: • 2.5 mg/kg for 1 dose, then 4 weeks later 1.9 mg/kg Q4W • Restart at 1.9 mg/kg Q8W after OEF resolution‡	90.5 (87.5-93.0)	57.0 (53.5-62.0)	77.3 (74.0-80.5)	66.5 (61.5-71.5)
2 planned step-downs: • 2.5 mg/kg for 1 dose, then 8 weeks later 1.9 mg/kg Q8W, then 1.9 mg/kg Q12W at Cycle 7 • Restart at 1.9 mg/kg Q12W after OEF resolution§	88.0 (85.0-90.0)	46.0 (42.5-50.0)	68.6 (65.4-71.8)	48.5 (42.5-53.0)

*The simulations implemented dose holds for OEFs of grade ≥2, and reinitiation of dosing at grade ≤1. Events reported here were simulated over a 50-month period.[21] †Dose reduction occurred only following OEFs of grade ≥3. ‡Modification to 1.9 mg/kg Q12W, then 1.4 mg/kg Q12W for subsequent events. §Modification to 1.4 mg/kg Q12W for subsequent events.

BVd, belantamab mafodotin, bortezomib, dexamethasone; FDA, Food and Drug Administration; OEF, ophthalmic examination finding; ORR, overall response rate; PFS, progression-free survival; PI, prediction interval; QxW, every x weeks; VGPR, very good partial response

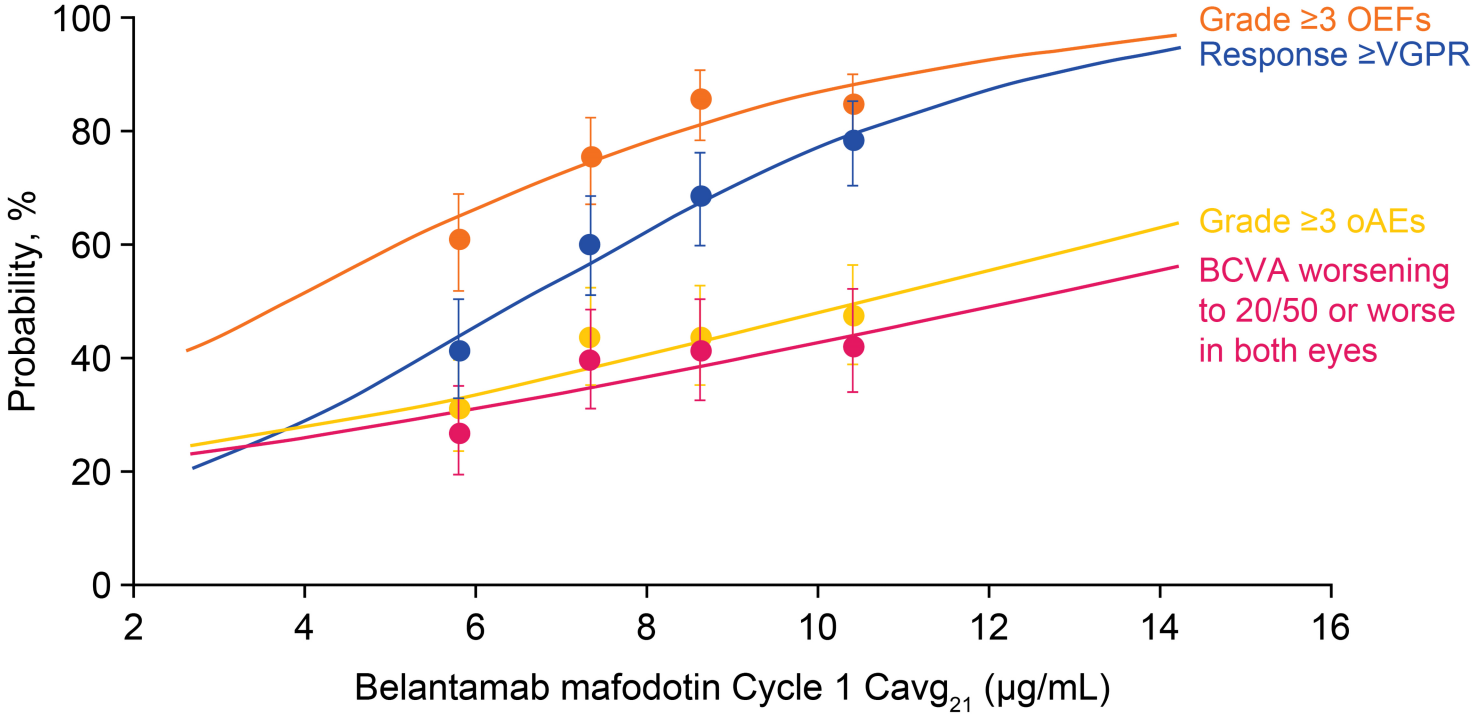
Figure 1. Integrated efficacy and safety exposure-response curves

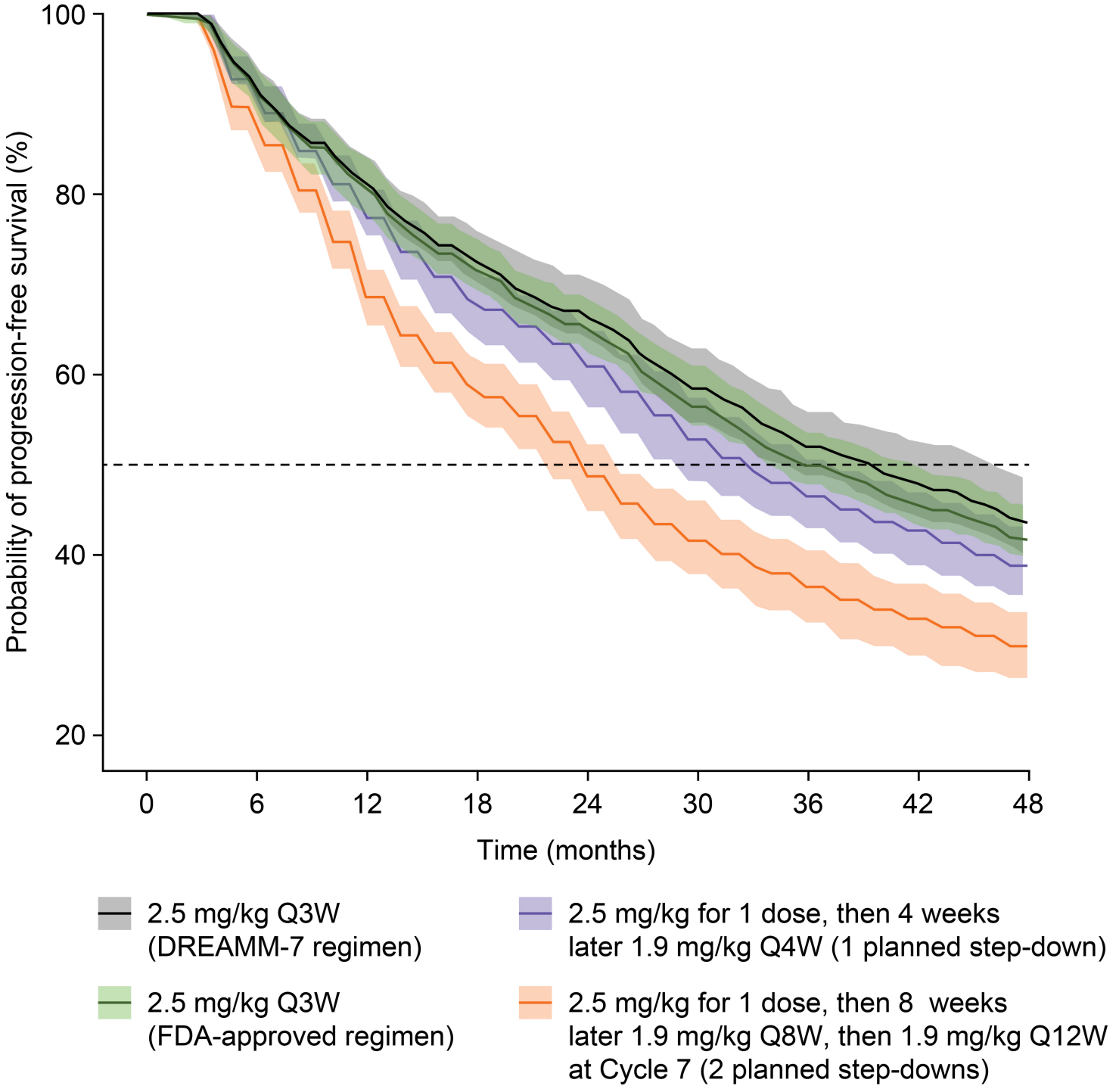
BCVA, best-corrected visual acuity; C_{avg21}, average concentration over 21 days; oAE, ocular adverse event; OEF, ophthalmic examination finding; VGPR, very good partial response

Figure 2. Predicted progression-free survival of different simulated dosing regimens for BVd

Note: Shaded areas represent the 95% prediction intervals.

BVd, belantamab mafodotin, bortezomib, dexamethasone; QxW, every x weeks


Probability, %
100
80
60
40
20
0
2
4
6
8
10
12
14
16
Belantamab mafodotin Cycle 1 Cavg21 (µg/mL)
Grade ≥3 OEFs
Response ≥VGPR
Grade ≥3 oAEs
BCVA worsening to 20/50 or worse in both eyes


100
80
60
40
20
Probability of progression-free survival (%)
0
6
12
18
24
30
36
42
48
Time (months)
2.5 mg/kg Q3W
(DREAMM-7 regimen)
2.5 mg/kg Q3W
(FDA-approved regimen)
2.5 mg/kg for 1 dose, then 4 weeks
later 1.9 mg/kg Q4W (1 planned step-down)
2.5 mg/kg for 1 dose, then 8 weeks
later 1.9 mg/kg Q8W, then 1.9 mg/kg Q12W
at Cycle 7 (2 planned step-downs)

Supplementary Materials

Methods

Covariates

Covariate assessments were performed to determine their potential impacts on exposure-response relationships. Assessments included demographic characteristics (age, sex, race, weight, body mass index, country), baseline clinical characteristics (albumin and immunoglobulin G [IgG] levels, renal and hepatic function), baseline disease characteristics (IgG-type myeloma, cytogenetic risk, levels of soluble B-cell maturation antigen [sBCMA], beta-2 microglobulin, and lactate dehydrogenase [LDH], International Staging System stage, Eastern Cooperative Oncology Group performance status, and extramedullary disease), therapy status (number of prior therapy lines, prior anti-CD38 or bortezomib treatment, refractory to immunomodulatory drug and proteasome inhibitor, and belantamab mafodotin schedule), and baseline safety-related covariates (history of dry eye, keratopathy presence, best-corrected visual acuity [BCVA], platelet level).

Stepwise covariate search

In the initial univariate step, individual covariates were included in the model to identify those significant at an alpha of 0.01. Significant covariates were taken into the stepwise search, where covariates were added to the model in order from most to least significant until all significant covariates at alpha 0.01 were included. For exposure measures, only the most significant measure was included. Subsequently, the effect of removing individual covariates from the model was assessed, with covariates retained if their removal resulted in a significant difference at the 0.001 alpha level. Once all nonsignificant covariates were removed, the final model was defined. If an exposure measure other than Cycle 1 average concentration over 21 days (C_{avg21}) was significant, a model replacing the exposure parameter with C_{avg21} was generated and superseded the other parameter if the fit was similar.

The following deltas (i.e., differences between dose levels or changes from the typical value) were used for the computation of odds or hazard ratios:

- Cycle 1 belantamab mafodotin concentration at the end of 21 days delta of 0.5 ug/mL, representing the difference between the predicted Cycle 1 belantamab mafodotin concentration at the end of 21 days for a dose of 2.5 mg/kg and a dose of 1.9 mg/kg.

- Cycle 1 belantamab mafodotin average concentration (C_{avg}) delta of 2.0 ug/mL, representing the approximate difference between the predicted Cycle 1 belantamab mafodotin C_{avg} for a dose of 2.5 mg/kg and a dose of 1.9 mg/kg.

- Cycle 1 belantamab mafodotin maximum concentration (C_{max}) delta of 4.0 ug/mL, representing the approximate difference between the predicted belantamab mafodotin C_{max} for a dose of 2.5 mg/kg and a dose of 1.9 mg/kg.

- Cycle 1 cysteine maleimidocaproyl monomethyl auristatin F (cys-mcMMAF) C_{max} delta of 0.22 ng/mL, representing the difference between the predicted cys-mcMMAF C_{max} for a dose of 2.5 mg/kg and a dose of 1.9 mg/kg.

- Cycle 1 cys-mcMMAF C_{avg} delta of 0.05 ng/mL, representing the difference between the predicted cys-mcMMAF C_{avg} for a dose of 2.5 mg/kg and a dose of 1.9 mg/kg.

- Baseline IgG delta of 3 g/L, representing a 20% change from the typical value.

- Baseline albumin delta of 8 g/L, representing a 20% change from the typical value.

- Baseline sBCMA delta of 20 ng/mL, representing a 40% change from the typical value.

- Baseline lactate dehydrogenase delta of 50 U/L, representing the approximate change from either the first quartile or third quartile to the median.

- Baseline platelet count delta of 25×10^9/L, representing the difference between each grade of thrombocytopenia.

Supplementary Table 1. Studies included in exposure-response analyses

Study	Study design
DREAMM-6 [1,2]	Phase 1/2, open-label, dose-escalation and dose-expansion study; belantamab mafodotin in combination with lenalidomide plus dexamethasone (BRd, Arm A), or bortezomib plus dexamethasone (Arm B) in patients with RRMM who received ≥1 prior therapy line *Belantamab mafodotin dosing*: Arm A (BRd): 1.9 mg/kg and 2.5 mg/kg as a single dose on Day 1 Q4W; 2.5 mg/kg administered as a 50:50 split dose on Day 1 and Day 8 Q4W; or 1.9 mg/kg Q8W as a single dose on Day 1 Arm B (BVd): 1.9 mg/kg Q3W; 2.5 mg/kg Q3W; 3.4 mg/kg Q3W; 2.5 mg/kg split (50% and 50% dose on Day 1 and Day 8) Q3W; 3.4 mg/kg split (50% and 50% dose on Day 1 and Day 8) Q3W; 1.9 mg/kg Q6W; 2.5 mg/kg Q6W; and 2.5 mg/kg in Cycle 1 followed by stepdown to 1.9 mg/kg Q6W
DREAMM-7[3,4]	Phase 3 study of BVd vs DVd in patients with RRMM who received ≥1 prior therapy line *Belantamab mafodotin dosing*: 2.5 mg/kg Q3W
DREAMM-8[5,6]	Phase 3 study of BPd vs PVd in patients with RRMM who received ≥1 prior therapy line including lenalidomide *Belantamab mafodotin dosing*: 2.5 mg/kg on Day 1 of Cycle 1 and 1.9 mg/kg in Cycle 2 and beyond Q4W

BPd, belantamab mafodotin, pomalidomide, dexamethasone; BRd, belantamab mafodotin, lenalidomide, dexamethasone; BVd, belantamab mafodotin, bortezomib, dexamethasone; DVd, daratumumab, bortezomib, dexamethasone; PVd, pomalidomide, bortezomib, dexamethasone; QxW, every x weeks; RRMM, relapsed/refractory multiple myeloma.

Supplementary Table 2. Summary of exposure-efficacy analyses

Endpoint	Univariate covariate	ΔOFV	Univariate p-value	Parameter	OR or HR (95% CI)
Probability of overall response	Belantamab mafodotin C_{max}	35.89	<0.0001	Belantamab mafodotin C_{avg21}	1.91 (1.49-2.47)
	Belantamab mafodotin C_{avg21}	35.41	<0.0001	Extramedullary disease	0.203 (0.109-0.374)
	Extramedullary disease	32.69	<0.0001		
	Baseline sBCMA	19.82	<0.0001		
	Baseline albumin	18.15	<0.0001		
	Prior anti-CD38 treatment	14.9	0.00011		
	Baseline LDH	13.89	0.00019		
	Baseline beta-2 microglobulin	13.87	0.0002		
	ISS stage I or stage II or stage III at screening	16.91	0.00021		
	Prior LOTs	15.38	0.00046		
	ECOG PS ≥1	8.41	0.0037		
	Baseline ECOG PS	10.55	0.0051		
Probability of ≥VGPR	Belantamab mafodotin C_{avg21}	53.62	<0.0001	Belantamab mafodotin C_{avg21}	2.09 (1.68-2.64)
	Extramedullary disease	52.22	<0.0001	Extramedullary disease	0.116 (0.0502-0.243)
	Prior anti-CD38 treatment	31.68	<0.0001	Prior anti-CD38 treatment	0.277 (0.167-0.455)
	Prior LOTs	28.46	<0.0001		
	Baseline albumin	19.73	<0.0001		
	>1 prior LOT	13.69	0.00022		
	Baseline sBCMA	13.46	0.00024		
	Baseline LDH	13.01	0.00031		
	Baseline IgG	11.36	0.00075		
	Baseline beta-2 microglobulin	8.98	0.0027		
Probability of ≥CR	Prior anti-CD38 treatment	38.26	<0.0001	Prior anti-CD38 treatment	0.146 (0.0683-0.282)

	Belantamab mafodotin C_{avg21}	28.57	<0.0001	Extramedullary disease	0.194 (0.065-0.469)
	Prior LOTs	30.93	<0.0001	Baseline IgG	0.895 (0.855-0.934)
	Baseline IgG	21.85	<0.0001		
	Extramedullary disease	19.53	<0.0001		
	>1 prior LOT	15.61	<0.0001		
	Baseline albumin	13.9	0.00019		
	Baseline LDH	12.43	0.00042		
	ECOG PS 2	8.33	0.0039		
	Black race	7.93	0.0049		
	Baseline beta-2 microglobulin	7.07	0.0078		
	Planned dosing schedule	13.52	0.0090		
Probability of MRD negativity (sCR/CR)	Prior LOTs	33.19	<0.0001	2/3 prior LOTs	0.686 (0.424, 1.1)
	Prior anti-CD38 treatment	29.46	<0.0001	≥4 prior LOTs	0.183 (0.0607, 0.446)
	>1 prior LOT	17.33	<0.0001	IgG type MM	0.44 (0.276, 0.702)
	Belantamab mafodotin C_{max}	11.5	0.00069	Prior anti-CD38 treatment	0.186 (0.0543, 0.482)
	Extramedullary disease	11.26	0.00079		
	Planned schedule	18.42	0.001		
	Baseline LDH	10.43	0.0012		
	IgG type MM	8.28	0.004		
	Baseline IgG	6.9	0.0086		
Progression-free survival	Prior anti-CD38 treatment	53.94	<0.0001	Prior anti-CD38 treatment	2.97 (2.18-4.05)
	Baseline LDH	46.53	<0.0001	Baseline sBCMA	1.05 (1.03-1.07)
	Prior LOTs	49.17	<0.0001	Extramedullary disease	2.33 (1.63-3.32)

	Baseline sBCMA	44.32	<0.0001	Baseline LDH	1.06 (1.03-1.09)
	Extramedullary disease	27.98	<0.0001		
	Belantamab mafodotin C_{max}	27.33	<0.0001		
	Baseline beta-2 microglobulin	22.11	<0.0001		
	Belantamab mafodotin C_{avg21}	20.69	<0.0001		
	>1 prior LOT	19.32	<0.0001		
	ISS stage I or stage II or stage III at screening	18.6	<0.0001		
	Planned dosing schedule	23.35	0.00011		
	Baseline albumin	11.46	0.00071		
	Refractory to both IMD and PI	6.71	0.0096		
Overall survival	Baseline LDH	46.27	<0.0001	Baseline LDH	1.08 (1.05-1.11)
	Baseline sBCMA	40.71	<0.0001	Extramedullary disease	2.24 (1.45-3.46)
	ISS stage I or stage II or stage III at screening	34.47	<0.0001	Baseline sBCMA	1.04 (1.02-1.06)
	Belantamab mafodotin C_{max}	30.22	<0.0001	Prior anti-CD38 treatment	2.25 (1.51-3.34)
	Baseline beta-2 microglobulin	26.8	<0.0001		
	Extramedullary disease	25.94	<0.0001		
	Belantamab mafodotin C_{avg21}	25.81	<0.0001		
	Prior anti-CD38 treatment	23.92	<0.0001		
	Baseline albumin	22.48	<0.0001		
	Prior LOTs	19.37	<0.0001		
	ISS stage I or stage II/III at screening	11.64	0.00064		
	Renal function	12.47	0.002		
	IgG type MM	7.97	0.0048		
	>1 prior LOT	7.83	0.0051		
	Refractory to both IMD and PI	6.8	0.0091		

	Baseline age	6.66	0.0099		
Duration of response	Prior anti-CD38 treatment	38.4	<0.0001	Prior anti-CD38 treatment	4.25 (2.88-6.27)
	Prior LOTs	29.97	<0.0001	Baseline sBCMA	1.06 (1.04-1.08)
	Baseline LDH	20.75	<0.0001		
	Baseline sBCMA	17.26	<0.0001		
	>1 prior LOT	15	0.0001		
	Baseline beta-2 microglobulin	7.15	0.0075		
Time to response	Belantamab mafodotin C_{tau21}	38.17	<0.0001	Belantamab mafodotin C_{avg21}	1.28 (1.14-1.43)
	Belantamab mafodotin C_{avg21}	29.21	<0.0001	Extramedullary disease	0.374 (0.243-0.577)
	IgG type MM	23.81	<0.0001	IgG type MM	0.562 (0.448-0.704)
	Extramedullary disease	21.42	<0.0001		
	Baseline IgG	20.03	<0.0001		
Time to best response	Prior anti-CD38 treatment	24.9	<0.0001	Prior anti-CD38 treatment	2.1 (1.6-2.74)
	Prior LOTs	13.46	0.0012		
	Belantamab mafodotin C_{tau21}	8.16	0.0043		
	Renal function	9.71	0.0078		
	Baseline LDH	7.01	0.0081		

For the univariate analyses, the top 3 covariates resulting in ΔOFV >6.63 relative to the null model were included. Additionally, any covariates resulting in a ΔOFV >10.83 were included. Only the strongest exposure covariate was included; if Cycle 1 belantamab mafodotin C_{avg} was not the strongest exposure covariate, it was included for reference and comparison across the efficacy and safety endpoints.

C_{avg21}, average concentration over 21 days; CI, confidence interval; C_{max}, maximum concentration; CR, complete response; C_{tau21}, concentration at the end of a cycle; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IgG, immunoglobulin G; IMD, immunomodulatory drug; ISS, International Staging System; LDH, lactate dehydrogenase; LOT, line of therapy; MM, multiple myeloma; MRD, minimal residual disease; OFV, objective function value; OR, odds ratio; PI, proteasome inhibitor; sBCMA, soluble B-cell maturation antigen; sCR, stringent complete response; ≥VGPR, very good partial response or better.

Supplementary Table 3. Summary of exposure-safety analyses

Endpoint	Univariate covariate	ΔOFV	Univariate p-value	Parameter	Odds ratio (95% CI)
Probability of grade ≥2 oAEs (CTCAE scale)	Baseline sBCMA	15.42	<0.0001	Baseline sBCMA	0.95 (0.923-0.975)
	Belantamab mafodotin C_{avg21}	15.27	<0.0001		
	Belantamab mafodotin C_{tau21}	12.66	0.0004		
	Cys-mcMMAF C_{avg21}	10.95	0.0009		
	Cys-mcMMAF C_{max}	10.54	0.0012		
	Planned schedule	17.47	0.0016		
Probability of grade ≥3 oAEs (CTCAE scale)	Baseline sBCMA	13.88	0.0002	Baseline sBCMA	0.943 (0.909-0.973)
	Cys-mcMMAF C_{max}	13.24	0.0003	European country	0.508 (0.354-0.728)
	European country	12.6	0.0004		
	Belantamab mafodotin C_{avg21}	10.73	0.0011		
	Belantamab mafodotin C_{tau21}	8.55	0.0035		
	Cys-mcMMAF C_{avg21}	8.49	0.0036		
	ISS stage I or stage II/III at screening	6.74	0.0094		
Probability of grade ≥2 OEFs (KVA scale)	Belantamab mafodotin C_{avg21}	51.61	<0.0001	Belantamab mafodotin C_{avg21}	2.38 (1.73-3.35)
	Belantamab mafodotin C_{tau21}	39.27	<0.0001	Baseline sBCMA	0.942 (0.912-0.971)
	Baseline sBCMA	35.65	<0.0001		
	Belantamab mafodotin C_{max}	29.56	<0.0001		
	Baseline albumin	25.84	<0.0001		
	Baseline LDH	17.39	<0.0001		
	Baseline beta-2 microglobulin	14.39	<0.000		
	Extramedullary disease	10.48	0.0012		
	ISS stage I or stage II or stage III at screening	12.21	0.0022		
	ECOG PS ≥1	8.57	0.0034		
	Cys-mcMMAF C_{avg21}	7.35	0.0067		
	ISS stage I or stage II/III at screening	7.3	0.0069		

Probability of grade ≥3 OEFs (KVA scale)	Baseline sBCMA	31.85	<0.0001	Baseline sBCMA	0.944 (0.915-0.971)
	Belantamab mafodotin C_{avg21}	31.41	<0.0001	Belantamab mafodotin C_{avg21}	1.6 (1.26-2.04)
	Belantamab mafodotin C_{max}	21.77	<0.0001		
	Belantamab mafodotin C_{tau21}	19.91	<0.0001		
	Baseline LDH	19.22	<0.0001		
	Baseline beta-2 microglobulin	15.95	<0.0001		
	ISS stage I or stage II or stage III at screening	16.84	0.0002		
	Extramedullary disease	12.76	0.0004		
	Prior anti-CD38 treatment	8.94	0.0028		
	Cys-mcMMAF C_{avg21}	8.65	0.0033		
	Cys-mcMMAF C_{max}	7.92	0.0049		
	Prior LOT	10.2	0.0061		
Probability of worsening of BCVA to 20/50 or worse in both eyes	Belantamab mafodotin C_{max}	13.66	0.0002	Baseline BCVA best eye, logMAR	2.34 (1.48-3.84)
	Baseline BCVA best eye, logMAR	13.24	0.0003	Belantamab mafodotin C_{avg21}	1.32 (1.1-1.6)
	Planned schedule	19.11	0.0007		
	Prior anti-CD38 treatment	10.74	0.0010		
	Baseline albumin	10.67	0.001		
	Baseline BCVA worst eye, logMAR	7.48	0.0062		
	Baseline LDH	7.44	0.006		
	Belantamab mafodotin C_{avg21}	6.88	0.0087		

For the univariate analyses, the top 3 covariates resulting in ΔOFV >6.63 relative to the null model were included. Additionally, any covariates resulting in a ΔOFV >10.83 were included. Only the strongest exposure covariate was included; if Cycle 1 belantamab mafodotin C_{avg} was not the strongest exposure covariate, it was included for reference and comparison across the efficacy and safety endpoints.

BCVA, best corrected visual acuity; BMI, body mass index; C_{avg21}, average concentration over 21 days; CI, confidence interval; C_{max}, maximum concentration; C_{tau21}, concentration at the end of a cycle; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; KVA, Keratopathy and Visual Acuity; LDH, lactate

dehydrogenase; LOT, line of therapy; mcMMAF, maleimidocaproyl monomethylauristatin F; oAE, ocular adverse event; OEF, ophthalmic examination finding; OFV, objective function value; sBCMA, soluble baseline B-cell maturation antigen.

Supplementary Table 4. Dose modifications predicted for simulated regimens

Belantamab mafodotin dosing regimen for BVd*	**Dose hold, % (95% PI)**	**Dose reduction, % (95% PI)**
Reference (DREAMM-7): • 2.5 mg/kg Q3W • Restart at 1.9 mg/kg Q3W after OEF resolution[†]	97.0 (94.5-99.0)	78.0 (74.0-82.0)
FDA-approved regimen: • 2.5 mg/kg Q3W • Restart at 1.9 mg/kg Q3W after OEF resolution (1.9 mg/kg Q8W for subsequent events)	96.5 (94.5-99.0)	85.5 (80.5-89.0)
1 planned step-down: • 2.5 mg/kg for 1 dose, then 4 weeks later 1.9 mg/kg Q4W • Restart at 1.9 mg/kg Q8W after OEF resolution[‡]	96.0 (93.5-98.5)	77.0 (72.5-81.5)
2 planned step-downs: • 2.5 mg/kg for 1 dose, then 8 weeks later 1.9 mg/kg Q8W, then 1.9 mg/kg Q12W at Cycle 7 • Restart at 1.9 mg/kg Q12W after OEF resolution[§]	85.5 (82.0-89.0)	69.0 (64.0-74.0)

*The simulations implemented dose holds for OEFs of grade ≥2, and reinitiation of dosing at grade ≤1.

[†]Dose reduction occurred only following OEFs of grade ≥3. Events reported here were simulated over a 50-month period.[7] [‡]Modification to 1.9 mg/kg Q12W, then 1.4 mg/kg Q12W for subsequent events.

[§]Modification to 1.4 mg/kg Q12W for subsequent events.

BVd, belantamab mafodotin, bortezomib, dexamethasone; FDA, Food and Drug Administration; OEF, ophthalmic examination finding; PI, prediction interval; QxW, every x weeks.

Supplementary Table 5. Predicted number of doses administered for simulated regimens

Belantamab mafodotin dosing regimen for BVd*	**Mean number of doses by time on treatment (95% PI)**		
	0-6 months	**6-12 months**	**12-24 months**
Reference (DREAMM-7): • 2.5 mg/kg Q3W • Restart at 1.9 mg/kg Q3W after OEF resolution†	4.0 (3.8-4.2)	3.1 (2.9-3.4)	5.7 (5.2-6.1)
FDA-approved regimen: • 2.5 mg/kg Q3W • Restart at 1.9 mg/kg Q3W after OEF resolution (1.9 mg/kg Q8W for subsequent events)	4.0 (3.8-4.2)	2.4 (2.2-2.6)	3.5 (3.2-3.7)
1 planned step-down: • 2.5 mg/kg for 1 dose, then 4 weeks later 1.9 mg/kg Q4W • Restart at 1.9 mg/kg Q8W after OEF resolution‡	3.3 (3.1-3.5)	2.0 (1.9-2.2)	3.5 (3.2-3.7)
2 planned step-downs: • 2.5 mg/kg for 1 dose, then 8 weeks later 1.9 mg/kg Q8W, then 1.9 mg/kg Q12W at Cycle 7 • Restart at 1.9 mg/kg Q12W after OEF resolution§	2.4 (2.3-2.5)	1.5 (1.4-1.6)	2.7 (2.6-2.9)

*The simulations implemented dose holds for OEFs of grade ≥2, and reinitiation of dosing at grade ≤1. †Dose reduction occurred only following OEFs of grade ≥3. ‡Modification to 1.9 mg/kg Q12W, then 1.4 mg/kg Q12W for subsequent events. §Modification to 1.4 mg/kg Q12W for subsequent events.

BVd, belantamab mafodotin, bortezomib, dexamethasone; FDA, Food and Drug Administration; OEF, ophthalmic examination finding; PI, prediction interval; QxW, every x weeks.

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