Exposure–Response Analyses for Therapeutic Dose Selection of Belantamab Mafodotin in Patients With Relapsed/Refractory Multiple Myeloma

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Belantamab mafodotin is an antibody–drug conjugate comprising a humanized anti-B-cell maturation antigen (BCMA) monoclonal antibody conjugated to monomethyl auristatin F (MMAF) via a protease-resistant maleimidocaproyl linker. Single-agent belantamab mafodotin showed clinically meaningful activity and manageable safety in patients with heavily pretreated relapsed/refractory multiple myeloma (RRMM) in the phase I DREAMM-1 and phase II DREAMM-2 studies and is approved by the US Food and Drug Administration and European Medicines Agency for RRMM treatment. To support monotherapy dose selection, the relationship between Cycle 1 exposure (derived using a population pharmacokinetic model) and clinical response (for multiple efficacy and safety end points) was explored. In DREAMM-2, efficacy end points (probability of response (PoR) and progression-free survival (PFS)) were associated with exposure in univariate evaluation; however, once disease burden factors were included in the model (e.g., baseline soluble BCMA, ß$_2$-microglobulin), exposure was no longer significant. Patients with higher disease burden had lower exposure. In DREAMM-1, belantamab mafodotin exposure was the only variable to correlate with PoR and PFS. Probability of corneal events (keratopathy), but not dry eye or blurred vision, was strongly associated with belantamab mafodotin exposure (DREAMM-2). Higher cys-mcMMAF maximum plasma drug concentration (C_{max}) and lower baseline platelet count were associated with increased probability of thrombocytopenia (DREAMM-1 and DREAMM -2). In general, safety end points were more strongly associated with belantamab mafodotin exposure than efficacy end points, particularly after disease factors and patient characteristics were taken into account. Overall, these findings supported the monotherapy dose recommendation of belantamab mafodotin as 2.5 mg/kg every 3 weeks in patients with RRMM who have received four or more prior therapies.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Single-agent belantamab mafodotin, an antibody–drug conjugate, demonstrated deep and durable clinical responses and manageable safety in patients with heavily pretreated relapsed/refractory multiple myeloma (RRMM).

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ To support dose selection, exposure–response analyses were performed to examine the relationship between Cycle 1 exposure and efficacy and safety end points.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ In DREAMM-2, efficacy end points were most associated with disease burden, while safety end points were associated with exposure. The impact of disease burden on exposure may have confounded the exposure–efficacy analysis. Overall, increases in exposure to belantamab mafodotin over the studied dose range in DREAMM-2 increased the probability of safety events without commensurate improvements in efficacy.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ This analysis helps our understanding of the exposure–response relationship between belantamab mafodotin dose, pharmacokinetics, efficacy and safety end points, and the impact of covariates. It supports the recommendation for the belantamab mafodotin monotherapy dose of 2.5 mg/kg in patients with RRMM and may help to inform future clinical development.

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Multiple myeloma (MM) is an incurable hematologic malignancy characterized by the uncontrolled accumulation of malignant plasma cells in the bone marrow.[1,2] Despite recent advances in the management of MM, many patients develop relapsed/refractory MM (RRMM) and are resistant to current standard-of-care options.[3] Therefore, novel, effective, and well-tolerated treatments are needed for this patient population that has a particularly poor prognosis.[4]

B-cell maturation antigen (BCMA) is a cell surface receptor that is expressed on all malignant plasma cells and is essential for their proliferation and survival.[5] Considering its selective expression and crucial role in oncogenesis, BCMA represents an ideal therapeutic target for RRMM.[2]

Belantamab mafodotin (Blenrep) is a first-in-class BCMA-targeting antibody–drug conjugate (ADC) comprising a humanized immunoglobulin (Ig) G1, afucosylated anti-BCMA monoclonal antibody (mAb) conjugated to a cytotoxic payload monomethyl auristatin F (MMAF, mafodotin) by a protease-resistant maleimidocaproyl linker.[2] Belantamab mafodotin has a multimodal mechanism of action that involves delivery of monomethyl auristatin F to MM cells in its function as an ADC.[2,6] Upon binding to the surface of BCMA-expressing cells, belantamab mafodotin is rapidly internalized, and the active cytotoxic drug (cysteine[cys]-mcMMAF) is released inside the cell, disrupting the microtubule network and leading to cell cycle arrest and apoptosis. A cascade of other immune-mediated antimyeloma responses is also triggered. The afucosylated mAb has increased binding to FcγRIIIa receptors and enhances recruitment and activation of immune effector cells, thereby promoting antibody-dependent cellular cytotoxicity and phagocytosis. Apoptosis of the target cell also leads to the release of biomarkers characteristic of immunogenic cell death as well as immune-dependent mechanisms of action.

In both the phase I DREAMM-1 (Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, Immunogenicity and Clinical Activity of GSK2857916) (NCT02064387) and the pivotal phase II DREAMM-2 (A Study to Investigate the Efficacy and Safety of Two Doses of GSK2857916 in Participants With Multiple Myeloma Who Have Failed Prior Treatment With an Anti-CD38 Antibody) (NCT03525678) studies, single-agent belantamab mafodotin (administered by intravenous infusion every 3 weeks (Q3W)) led to deep and durable responses with a manageable safety profile in patients with heavily pretreated RRMM.[7–9] DREAMM-2 examined a more heavily pretreated population than DREAMM-1, and patients received belantamab mafodotin as a frozen liquid presentation at doses of either 2.5 mg/kg (n = 95) or 3.4 mg/kg (n = 99) Q3W.[7] The overall response rate (ORR) was 31% at 2.5 mg/kg and 34% at 3.4 mg/kg, with a deep response (very good partial response or better) achieved in 60% and 59%, respectively, of these responding patients.[10] Median duration of response (DoR) was not reached at the time of the primary analysis, but was 11.0 and 6.2 months for belantamab mafodotin 2.5 mg/kg and 3.4 mg/kg, respectively, after 13 months of follow-up.[11] The most common adverse events (AEs) reported in DREAMM-1 and DREAMM-2 were corneal events (microcyst-like epithelial changes, defined as corneal epithelium changes identified on slit-lamp eye examination, with or without symptoms),[7–9] and hematologic events (notably, thrombocytopenia and anemia). A refrigerated lyophilized powder presentation was also evaluated at the dose of 3.4 mg/kg (n = 24, ORR of 52%) in DREAMM-2 to gain clinical experience with the presentation intended for future clinical and commercial use. This presentation of belantamab mafodotin was developed to improve supply chain robustness by eliminating frozen shipments and storage; it was demonstrated analytically to be comparable to the frozen liquid presentation.[10]

The pharmacokinetics of belantamab mafodotin and cys-mcMMAF were investigated in 291 patients with RRMM who participated in DREAMM-1 (N = 73) and in DREAMM-2 (N = 218). Belantamab mafodotin pharmacokinetics were well described by a linear, two-compartment population pharmacokinetic (popPK) model, with a time-varying decrease in clearance.[12] At Cycle 1, belantamab mafodotin had a systemic clearance of 0.92 L/day, steady-state volume of distribution of 10.8 L, and an elimination half-life of 12 days. Over time, clearance was reduced by 28%, resulting in an elimination half-life of 14 days.[12] No clinically significant differences in the pharmacokinetics of belantamab mafodotin were observed based on age, sex, race, body weight, mild or moderate renal impairment, or mild hepatic impairment. Higher serum levels of ß$_2$-microglobulin, and soluble BCMA (sBCMA) and lower levels of albumin are associated with more advanced multiple myeloma or a higher multiple myeloma disease burden.[13–15] Higher baseline IgG and sBCMA levels, and lower baseline albumin levels were associated with higher belantamab mafodotin clearance leading to lower average and trough concentrations (C_{tau}).[12]

Single-agent belantamab mafodotin was recently approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of patients with RRMM who have received four or more prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.[16,17] The approved dose is 2.5 mg/kg, which was selected over the 3.4 mg/kg dose based on a more favorable tolerability and pharmacokinetic profile with similar efficacy in DREAMM-2.[7] Here we report the results of the exposure–response analyses in which we explored the relationship between exposure of belantamab mafodotin and cys-mcMMAF and response (efficacy and safety, including adverse events of special interest) using exposure measures from a PopPK model in support of the dose selection of single agent belantamab mafodotin; detailed methodology for the PopPK model development are described in a companion publication.[12]

METHODS

Data sources and PopPK modeling

The study designs of DREAMM-1 and DREAMM-2 have been reported previously;[8,9,18] details are summarized in **Table S1**. The DREAMM-1 study data as of August 31, 2018 and the DREAMM-2 study data as of June 21, 2019 were utilized for these analyses. Both studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines following approval by ethics committees and institutional review boards at each study site. All patients provided written informed consent.

For PK measurements, blood samples were collected pre-belantamab mafodotin and post-belantamab mafodotin dosing from all 73 patients in DREAMM-1 and all 218 patients in DREAMM-2 (sampling schedules shown in **Table S1**) and were analyzed for ADC, total mAb, cys-mcMMAF, and free sBCMA concentrations. The ADC assay quantified both free ADC and ADC bound to sBCMA; the total mAb assay quantified monoclonal antibody, with or without cys-mcMMAF, free or bound to sBCMA. All patients with at least one quantifiable ADC plasma concentration were included. These data were used to develop the PopPK model that generated *post hoc* Cycle 1 exposure measurements for ADC (maximum concentration (C_{maxa}), average concentration (C_{avga}), concentration at the end of the 21-day dosing interval (C_{taua})), and cys-mcMMAF (C_{maxm} and C_{avgm}). The PopPK model also identified covariates of clinical interest; it was noted that disease burden-related factors (e.g., sBCMA, IgG, and albumin levels) were found to impact clearance of the ADC, leading to lower exposures for patients with higher disease burden.[12]

End points

Efficacy. The relationship between exposure of the ADC and cys-mcMMAF and the following efficacy end points was assessed: ORR (partial response or better), progression-free survival (PFS), probability of response (PoR), time to response (TTR), time to best response (TTBR), and DoR. Disease assessments were performed Q3W in DREAMM-1 and DREAMM-2 (relative to the schedule of doses received, accounting for any dose delays),[18] in accordance with International Myeloma Working Group (IMWG) uniform response criteria.[15,19] Responses were assessed by investigators in DREAMM-1 and by investigators and an independent review committee in DREAMM-2.

Safety. Baseline and subsequent ophthalmic examinations were conducted before dosing and Q3W by an ophthalmologist or optometrist. In DREAMM-2, corneal events were evaluated and graded using the keratopathy and visual acuity (KVA) scale, which incorporates the severity of the microcyst-like epithelial changes (observed on examination with or without symptoms) and changes in best-corrected visual acuity (BCVA) as measured by the Snellen scale.[20] This scale was not available for DREAMM-1. Keratopathy events were also recorded as an AE and graded per Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03.[21] Definite worsening in BCVA in the better-seeing eye (≥ 0.3 change in Logarithm of the Minimum Angle of Resolution) and unilateral or bilateral worsening in BCVA to 20/50 or worse were also evaluated based on the Snellen Test in DREAMM-2.

Other AEs (e.g., thrombocytopenia, neutropenia, blurred vision, and dry eye) were graded according to National Cancer Institute (NCI)–Common Terminology Criteria for Adverse Events (CTCAE) version 4.0[22] in DREAMM-1 and CTCAE version 4.03 in DREAMM-2.[21]

The relationship between exposure and the following safety end points was assessed: probability of grade ≥ 2 or ≥ 3 corneal events and time to first event of grade ≥ 2 or ≥ 3 corneal events (DREAMM-2), probability of any grade or grade ≥ 2 keratopathy, blurred vision and dry eye (DREAMM-2), and probability of grade ≥ 3 thrombocytopenia or neutropenia and probability of occurrence of infusion-related reaction in Cycle 1 (both studies).

Exposure–response analyses

Efficacy exposure–response analyses were conducted separately for DREAMM-1 and DREAMM-2 based on the differences in methodology used to assess response. The primary analysis was based on the frozen liquid presentation cohorts of DREAMM-1 (n = 73, 0.03–3.4 mg/kg) and DREAMM-2 (n = 95 for 2.5 mg/kg; n = 99 for 3.4 mg/kg). Analysis of the lyophilized presentation cohort (n = 24) from the DREAMM-2 study was also carried out.

Statistical and graphical analyses were performed to assess the relationship between exposure measures and efficacy and safety end points in DREAMM-1 and DREAMM-2 (taking into account any covariates of significant clinical interest). The covariates of potential interest included demographics (sex, race, age, and weight), disease-related factors (e.g., International Staging System stage; baseline sBCMA, IgG, β_2-microglobulin, albumin; number of prior MM therapies; and type of prior MM therapy), eye-related factors (e.g., presence of keratopathy at baseline, history of dry eye, and history of eye surgery), and other variables (e.g., baseline platelet count, baseline neutrophil count, and lyophilized presentation).

Time-to-event end points (efficacy and safety) were evaluated with Kaplan-Meier plots (using quartiles of exposure) and Cox proportional hazard models using baseline covariates and Cycle 1 exposures as continuous variables. Univariate Cox proportional hazard modeling identified the strongest individual associations of exposure and other relevant covariates in terms of change in objective function. Formal covariate selection was performed using a stepwise forward inclusion ($P < 0.01$) and backwards elimination method ($P < 0.001$) to determine the final multivariate model (further details in **Supplementary Methods**).

Logistic regression modeling was used to explore the relationship between exposure and PoR or probability of occurrence of an adverse event, such as grade ≥ 2 or ≥ 3 corneal event as a function of ADC C_{tau}. The same covariate selection criteria were used to define the full and final models, as described in **Supplementary Methods**. For these analyses, a typical patient was defined as a 65-year-old male weighing 75 kg with mild renal impairment, normal liver function, and median baseline levels of sBCMA (100 ng/mL), IgG (10 g/L), and albumin (40 g/L).

RESULTS

Baseline patient characteristics

Baseline patient characteristics by cohort for the DREAMM-1 and DREAMM-2 studies are presented in **Table S2**.

Exposure–response efficacy analysis

Exposure–response analyses for efficacy end points were performed for the ADC and cys-mcMMAF (**Figure 1**) exposure measures. There was a strong positive correlation between ADC C_{avg} and ADC C_{tau} as well as between cys-mcMMAF C_{max} and cys-mcMMAF C_{avg} across the DREAMM-2 (frozen liquid presentation cohort) population (**Figure S1**).

Probability of response. In DREAMM-2 (frozen liquid presentation cohort), the number of patients achieving a partial response or better appeared to increase (with a deepening of responses) with higher exposure (**Figure 2a**), but patients with higher exposure also tended to have a lower disease burden, as clearance was found to be associated with disease burden markers.[12] Univariate analyses identified an inverse relationship between baseline sBCMA and baseline IgG and PoR and a positive relationship between belantamab mafodotin C_{tau} and PoR; however, the final model only retained baseline sBCMA (**Table 1**). Lower baseline sBCMA was associated with higher belantamab mafodotin exposure[12] and higher probability of response. When evaluating the trend for each quartile of sBCMA, limited responses were seen in the upper quartile of sBCMA. The exposure–response analysis was thus also performed on the lowest three quartiles of sBCMA; in this analysis, the final model only contained belantamab mafodotin

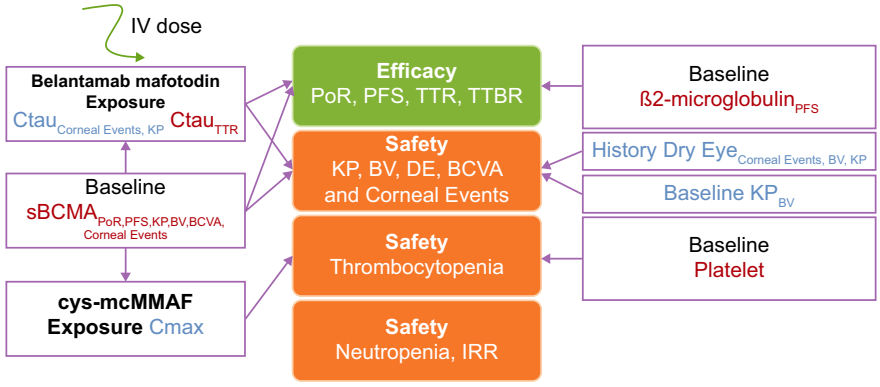

Figure 1 Exposure–response model schema with covariates (DREAMM-2 frozen liquid presentation). Significant covariates with positive relationship (blue) or negative relationship (red) are shown in the purple boxes. BCVA, best corrected visual acuity; BV, blurred vision; C_{max}, maximum concentration; Ctau, concentration on day 21; cys-mcMMAF, cysteine maleimidocaproyl monomethyl auristatin F; DE, dry eye; IgG, immunoglobulin G; IRR, infusion-related reaction; IV, intravenous; KP, keratopathy (National Cancer Institute–Common Toxicity Criteria for Adverse Events NCI-CTCAE Scale); PFS, progression-free survival; PoR, probability of response; sBCMA, soluble B-cell maturation antigen; TTBR, time to best response; TTR, time to response.

C_{tau} (**Table 1**). This model was similar to the one developed for the DREAMM-1 study, where the final model also only contained belantamab mafodotin C_{tau} (**Table 1**).

Progression-free survival. In DREAMM-2 (frozen liquid presentation), based on the Kaplan-Meier analysis, PFS tended to be longer with higher belantamab mafodotin C_{tau} (**Figure 2b**). While belantamab mafodotin C_{tau} was found to be associated with PFS in the univariate analysis, the final model showed that higher baseline sBCMA and β_2-microglobulin led to shorter PFS for DREAMM-2; PFS was related to the natural log of belantamab mafodotin C_{tau} for DREAMM-1 (**Table S3**).

Time to response and time to best response. For DREAMM-2 (frozen liquid presentation), TTR, but not TTBR, was found to be inversely related to belantamab mafodotin C_{tau} (**Figure 3**). Across belantamab mafodotin C_{tau} quartiles, there was separation in TTR between the upper two and lower two quartiles of exposure. The median time to response of quartile 4 was ≤ 1 month and for quartile 2 the median time to response was ≤ 2.5 months). For the DREAMM-1 study, neither TTR nor TTBR were found to be associated with any exposure metrics.

Duration of response. DoR was immature at the time of the primary data analyses for DREAMM-2, as the median DoR had not yet been reached; therefore, this analysis was not performed. For DREAMM-1, no trend was observed with exposure metrics, and the final model was the null model.

Exposure–response safety analysis

Corneal events. In the DREAMM-2 study (frozen liquid presentation), a higher frequency of corneal events (KVA scale) was observed with increased exposure quartile of belantamab mafodotin C_{tau}, along with a trend for higher-grade events (**Figure 4a**). Logistic regression analysis showed that the probability of a grade ≥ 2 and grade ≥ 3 corneal event (KVA scale) with belantamab mafodotin was significantly inversely related to baseline sBCMA. The probability of a grade ≥ 2 corneal event was inversely related to baseline sBCMA and positively related to a history of dry eye (**Table 2**).

The median time to first grade ≥ 2 corneal event (KVA scale) in DREAMM-2 was shorter for the two higher quartiles of belantamab mafodotin exposure (C_{tau}) than the lower quartiles, being ~ 21 days for quartile 4 and 63 days for quartile 1 (**Figure 4b**). Median time to the first grade ≥ 3 corneal event was 1–2 cycles longer for each quartile than for grade ≥ 2 events (~ 42 days and 100 days for quartiles 4 and 1, respectively) (**Figure 4c**). Cox proportional hazard modeling showed that the strongest predictor of time to grade ≥ 3 event was the natural log of belantamab mafodotin C_{tau}.

The probability of blurred vision of any NCI-CTCAE grade in DREAMM-2 was inversely related to baseline sBCMA and positively related to a history of dry eye; probability of grade ≥ 2 blurred vision was inversely related to sBCMA and positively associated with the presence of keratopathy (graded by NCI-CTCAE scale) at baseline. The probability of dry eye events was inversely related to baseline sBCMA.

Higher belantamab mafodotin C_{tau} in DREAMM-2 was not found to be associated with probability of occurrence or timing of first occurrence of definite worsening in BCVA or with unilateral or bilateral worsening in BCVA to 20/50 or worse. Lower baseline sBCMA level was associated with a higher probability of most of these end points, with some showing an earlier occurrence. No other covariates were identified for these end points.

Hematologic events and infusion-related reactions. In DREAMM-1 and DREAMM-2, lower baseline platelet count and higher cys-mcMMAF C_{max} were associated with increased probability of grade ≥ 3 thrombocytopenia, with the former being the strongest predictor (**Table 2** and **Figure S2**). No covariates were associated with the probability of grade ≥ 3 neutropenia or infusion-related reaction in Cycle 1 (data not shown).

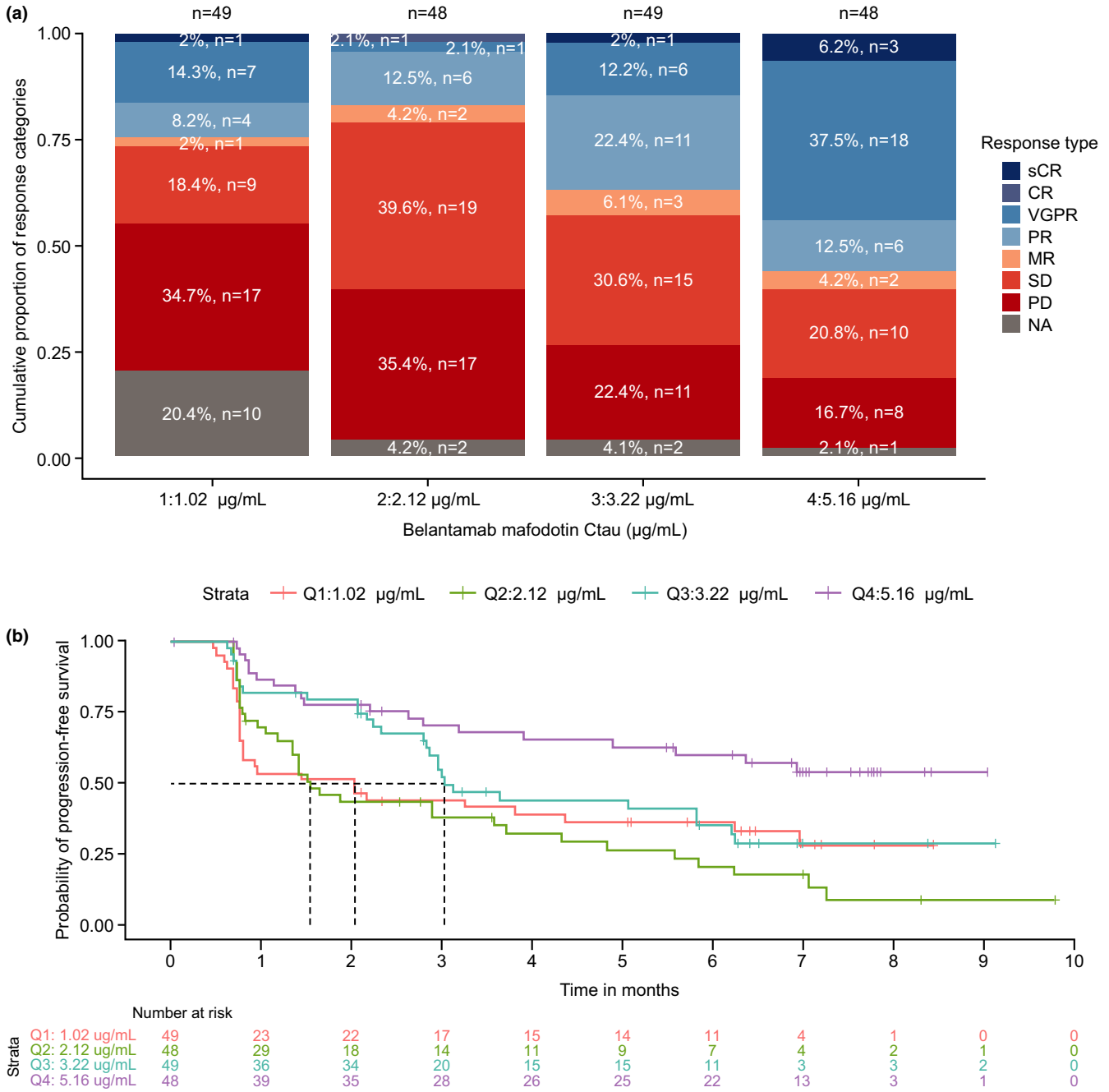

Figure 2 Probability of response and progression-free survival efficacy analyses. (**a**) Best response by Cycle 1 belantamab mafodotin C_{tau} (DREAMM-2; frozen liquid presentation); (**b**) PFS stratified by quartile of Cycle 1 belantamab mafodotin C_{tau} (DREAMM-2; frozen liquid presentation). Mean (min-max) for each belantamab mafodotin C_{tau} quartile: Q1: 1.02 (0.283, 1.51); Q2: 2.12 (1.53, 2.75); Q3: 3.22 (2.78, 3.76); Q4: 5.16 (3.77, 9.64). ADC, antibody–drug conjugate; CR, complete response; C_{tau}, concentration at the end of the dosing interval (Day 21); MR, minimal response; NA, not applicable; PD, progressive disease; PFS, progression-free survival; PR, partial response; Q, quartile; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

Integrated exposure–response analysis. **Figure 5** shows the probability of corneal events and PoR as a function of ADC C_{tau}. Higher belantamab mafodotin C_{tau} in DREAMM-2 was associated with the probability of developing grade ≥ 2 or grade ≥ 3 corneal events and inversely correlated with time of onset. At the predicted exposure for a typical patient receiving belantamab mafodotin 2.5 mg/kg (2.2 µg/mL), the estimated rates of grade ≥ 3 corneal events were ~ 10% higher than the efficacy rates. However, at the predicted exposure for a typical patient receiving belantamab mafodotin 3.4 mg/kg (3.0 µg/mL), the estimated rates of grade ≥ 3 corneal events were ~ 20% higher than the efficacy rates, with nonoverlapping 95% confidence intervals, reflecting the steeper slopes of the corneal event curves compared with the exposure efficacy curve in this dose range. There was

Table 1 Probability of response using final logistics regression model

Covariate	Beta (β)	SE	95% CI	dOFV	Delta	OR (95% CI)
Model with all FL data (DREAMM-2 FL presentation)						
Intercept (β_0)	0.109	0.223	−0.325, 0.551	NA	NA	NA
BSBCMA	−0.00608	0.00153	−0.00937, 0.00335	26.7	20	0.886 (0.829, 0.935)
Model with lowest 3 quartiles of sBCMA (DREAMM-2 FL presentation)						
Intercept (β_0)	−1.41	0.386	−2.20, −0.676	NA	NA	NA
C_{TAUA}	0.334	0.107	0.133, 0.556	11.1	0.8	1.31 (1.11, 1.56)
Model for DREAMM-1						
Intercept (β_0)	−2.06	0.535	−3.22, −1.1	NA	NA	NA
C_{TAUA}	0.341	0.0955	0.173, 0.548	21.5	0.8	1.31 (1.15, 1.55)

Logistic regression
Ln (p/(1−p)) = β_0 + β_x β X (where X is BSBCMA or C_{TAUA} as appropriate).

PoR using the final logistics regression model (DREAMM-1 and DREAMM-2 frozen liquid presentation).
BCMA, B-cell maturation antigen; BSBCMA, baseline soluble BCMA; CI, confidence interval; C_{TAUA}, antibody–drug conjugate trough concentration; dOFV, drop in objective function relative to the previous model; FL, frozen liquid; NA, not applicable; OR, odds ratio; PoR, probability of response; sBCMA; soluble B-cell maturation antigen; SE, standard error.

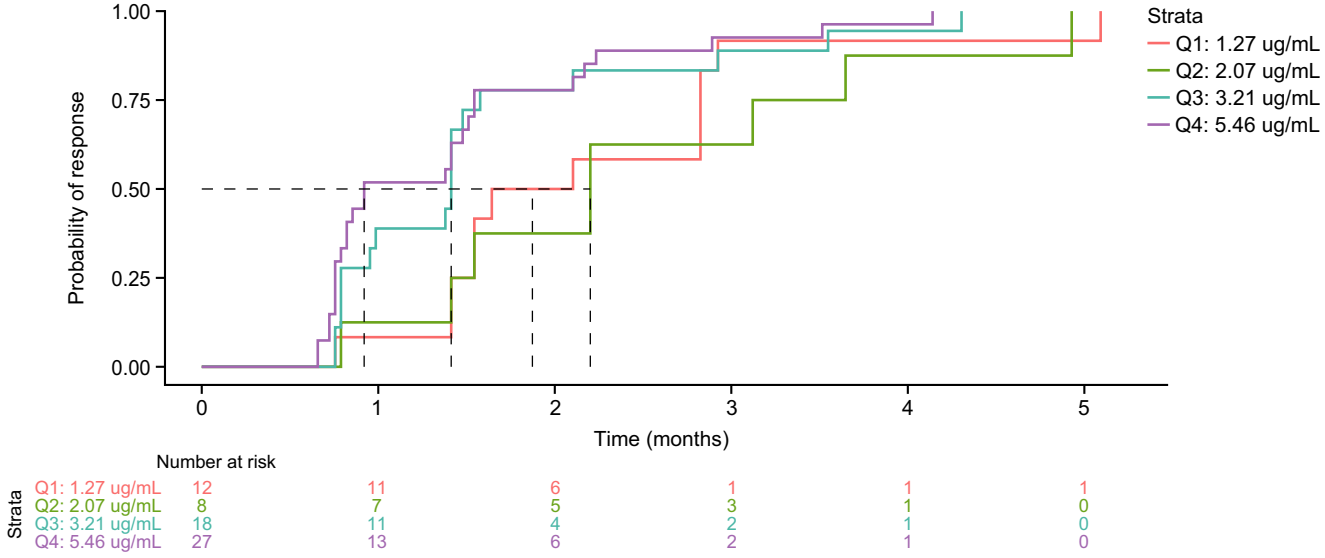

Figure 3 Time to response efficacy analysis. TTR stratified by quartile of Cycle 1 belantamab mafodotin C_{tau} (DREAMM-2; frozen liquid presentation). Mean (min-max) for each belantamab mafodotin C_{tau} quartile: Q1: 1.27 (0.878, 1.51); Q2: 2.07 (1.60, 2.75); Q3: 3.21 (2.78, 3.67); Q4: 5.46 (3.77, 9.64). C_{tau} concentrations represent those of responders within their respective original quartiles only. C_{tau}, concentration at the end of the dosing interval (Day 21); Q, quartile; TTR, time to response.

no increase in the probability of experiencing blurred vision or dry eye.

Lyophilized presentation

Combined analysis of DREAMM-2 including both the frozen liquid and lyophilized presentation cohorts showed that the relationships between exposure and efficacy and safety were consistent with the observed profiles using the frozen liquid presentation cohort only (data not shown). However, due to patient disease characteristics, the median exposure was higher with the lyophilized presentation (**Figure 5**).

DISCUSSION

Finding the balance between clinical benefit for patients achieved with a therapeutic agent vs. the incidence of dose/efficacy-limiting AEs is a key concern for all drug modalities.[23] Based on the primary analysis and exposure–response results of DREAMM-2, the 2.5 mg/kg dose of belantamab mafodotin was selected as the recommended dose for future studies in RRMM on the basis of its similar antimyeloma activity with a more favorable safety profile (i.e., less frequent dose modifications and a lower incidence of thrombocytopenia, bleeding, neutropenia, and infections) compared with the 3.4 mg/kg dose.[7] Assessing the benefit–risk profile

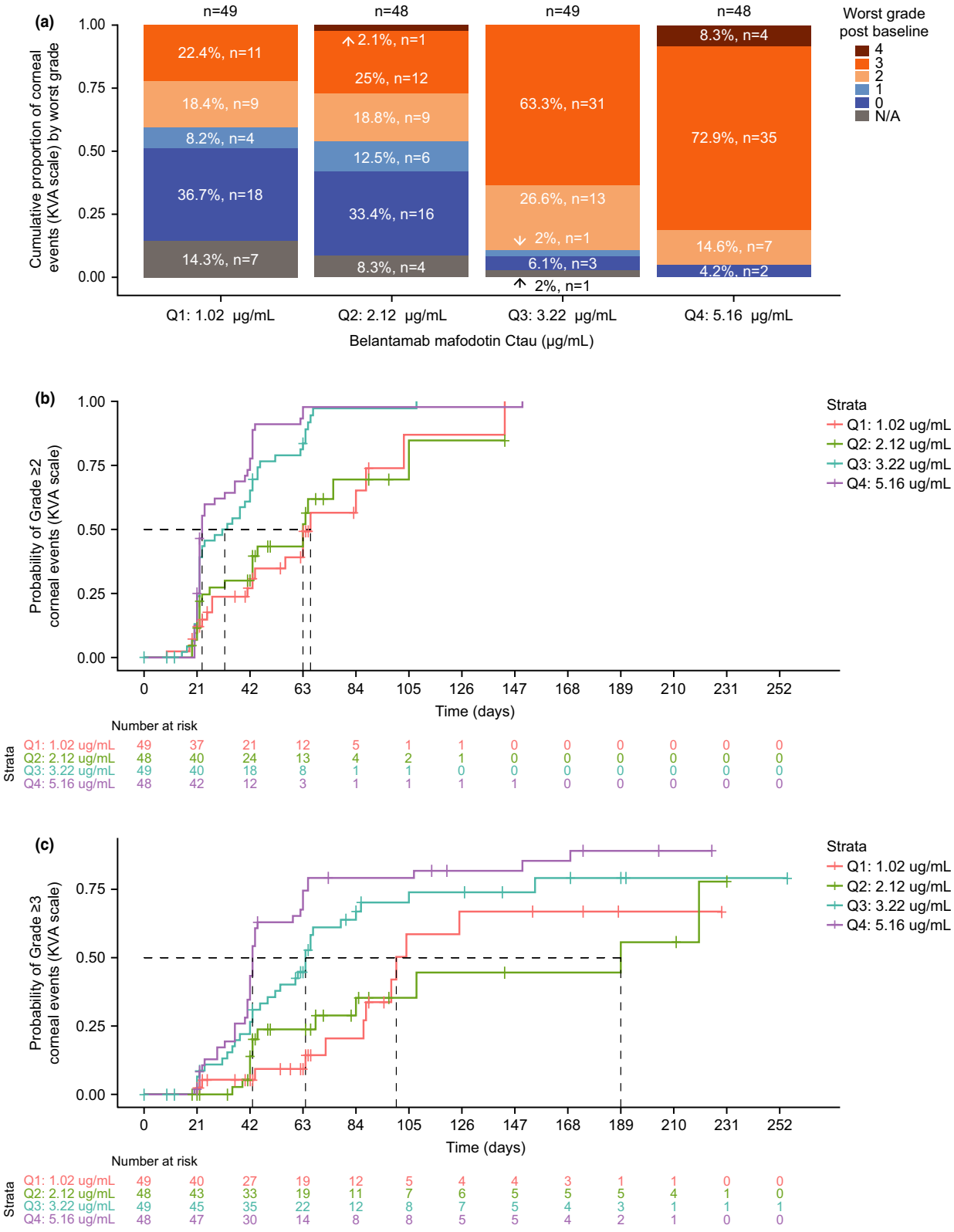

Figure 4 Exposure–response corneal events safety analysis; (**a**) Maximum grade of corneal event (KVA scale) by quartile of Cycle 1 belantamab mafodotin C_{tau} (DREAMM-2; frozen liquid presentation); time to first (**b**) grade ≥ 2 or (**c**) grade ≥ 3 corneal event (KVA scale) by quartile of Cycle 1 belantamab mafodotin C_{tau} (DREAMM-2, frozen liquid presentation). **a** mean (min–max) for each belantamab mafodotin C_{tau} quartile: Q1, 1.02 (0.28, 1.51); Q2, 2.12 (1.53, 2.75), Q3, 3.22 (2.78, 3.76); Q4, 5.16 (3.77, 9.64). **b** and **c** mean (min–max) for four belantamab mafodotin C_{tau} strata are as follows: Q1: 1.02 (0.283, 1.51); Q2: 2.12 (1.53, 2.75); Q3: 3.22 (2.78, 3.76); Q4: 5.16 (3.77, 9.64). ADC, antibody–drug conjugate; C_{tau}, concentration at the end of the dosing interval (Day 21); KVA, keratopathy and visual acuity; N/A, not applicable; Q, quartile.

Table 2 Probability of grade ≥ 2 or grade ≥ 3 corneal event and grade ≥ 3 thrombocytopenia - final logistic regression models

Covariate	Beta (β)	SE	95% CI	dOFV	Delta	OR (95% CI)
Probability of grade ≥ 2 corneal event						
Intercept (β_0)	−1.56	0.57	(−2.71, −0.47)	NA	NA	NA
C_{TAUA}	1.18	0.22	(0.78, 1.65)	63.3	0.8	2.58 (1.87, 3.74)
HISTDRYEYE	2.20	0.62	(1.06, 3.53)	13.1	1	9.04 (2.88, 34)
BSBCMA	−0.004	0.001	(−0.007, −0.002)	19.7	20	0.92 (0.87, 0.96)
Logistic regression: Ln (p/(1−p)) = $\beta_0 + \beta_{C_{TAUA}} \cdot C_{TAUA} + \beta_{HISTDRYEYE} \cdot$ HISTDRYEYE + $\beta_{BSBCMA} \cdot$ BSBCMA						
Probability of grade ≥ 3 corneal event						
Intercept (β_0)	−0.81	0.48	(−1.77, 0.12)	NA	NA	NA
C_{TAUA}	0.55	0.14	(0.30, 0.83)	46.2	0.8	1.55 (1.27, 1.93)
BSBCMA	−0.005	0.001	(−0.008, −0.003)	21.1	20	0.9 (0.85, 0.95)
Logistic Regression: Ln (p/(1−p)) = $\beta_0 + \beta_{C_{TAUA}} \cdot C_{TAUA} + \beta_{BSBCMA} \cdot$ BSBCMA						
Probability of grade ≥ 3 thrombocytopenia						
Intercept (β_0)	−8.87	3.41	(−15.9, −2.43)	NA	NA	NA
BPLAT	−0.0221	0.00375	(−0.03, −0.0152)	59.9	25	0.575 (0.472, 0.683)
LNCMAXM	1.59	0.493	(0.67, 2.62)	12.0	0.3	1.61 (1.22, 2.19)
Logistic regression: Ln (p/(1−p)) = $\beta_0 + \beta_{BPLAT} \cdot$ BPLAT + $\beta_{LNCMAXM} \cdot$ LNCMAXM						

Probability of grade ≥ 2 or grade ≥ 3 corneal event (KVA scale) logistic regression analysis parameters for Cycle 1 belantamab mafodotin Ctau and grade ≥ 3 thrombocytopenia logistic regression analysis parameters for baseline platelet count (DREAMM-2, frozen liquid presentation); BPLAT, baseline platelet count; BSBCMA, baseline soluble B-cell maturation antigen; CI, confidence interval; C_{TAUA}, antibody–drug conjugate trough concentration; dOFV, drop in objective function relative previous model with covariate added before it; HISTDRYEYE, history of dry eye; KVA, keratopathy and visual acuity; LNCMAXM, natural log of cys-mcMMAF maximum concentration; NA, not applicable; OR, odds ratio; SE, standard error.

with estimated exposure–response measures provides an additional tool for determining appropriate dosing for new therapies.

Increased disease and/or antigen burden has been linked to reduced exposure with other mAbs.[24–26] Using the PopPK model[12] to perform exposure–response analyses, belantamab mafodotin C_{tau} was a significant factor for PoR when evaluated independently of other factors. However, it was no longer significant in DREAMM-2 with its limited range of doses after accounting for disease burden-related factors (i.e., the decrease in the PoR linked to increased baseline sBCMA). Similarly, PFS tended to be longer with higher belantamab mafodotin exposure but was inversely related to baseline sBCMA and β_2-microglobulin. Thus, higher levels of baseline sBCMA generally led to reduced responses and shorter PFS, and belantamab mafodotin exposure was not retained in the final models for PoR or PFS. Higher levels of sBCMA have been shown to correlate to reduced responses in previous MM studies, irrespective of treatment option.[14] Therefore, baseline disease characteristics can have a confounding effect on efficacy exposure–response analyses, which makes it challenging to identify the independent contribution of exposure on treatment efficacy, especially when a narrow range of doses are studied. Studying a wider dose range, as was the case in DREAMM-1, or a subset of patients more likely to respond overcame this confounding effect and allowed for the identification of exposure as the key driver for efficacy. Similar confounding has been observed for other antibody therapeutics, where disease characteristics such as the IgG myeloma isotype or increased nonspecific mAb catabolism (due to higher disease burden) have been shown to increase clearance and reduce response.[24,26,27]

The exposure–response analyses for DREAMM-2 (2.5 and 3.4 mg/kg frozen liquid presentation) found that safety outcomes were impacted by belantamab mafodotin exposure. In DREAMM-2, the probability of grade ≥ 2 or grade ≥ 3 corneal events (KVA scale) increased with belantamab mafodotin C_{tau}. Ocular toxicity has been reported for other monomethyl auristatin-F–based ADCs for a variety of targets with noncleavable linkers[28,29] and may be caused by uptake of the ADC via nonspecific endocytosis into normal corneal epithelial cells.[20,30] Free cys-mcMMAF has low cell membrane permeability, which suggests that belantamab mafodotin exposure is likely the key driver for these corneal events. Higher belantamab mafodotin C_{tau} was not associated with definite worsening in BCVA, unilateral or bilateral worsening in BCVA to 20/50 or worse, or blurred vision or dry eye. Higher cys-mcMMAF C_{max} and lower baseline platelet count were associated with increased probability of thrombocytopenia.

Inclusion of the lyophilized cohort from DREAMM-2 in the exposure–response analyses led to similar PoR and PFS findings as observed for the frozen liquid presentation. However, as previously reported,[10] including disease burden and patient characteristics in the PopPK models was key to further interpretation of results for the lyophilized presentation cohort. They indicated that differences in exposure were consistent with differences in baseline factors such as sBCMA and albumin. These differences in exposure led to differences in efficacy and safety and can be explained by the same exposure–response relationships.

While preclinical data for belantamab mafodotin suggest that the conjugated cys-mcMMAF is the primary mechanism of action, the additional contribution of Fc-enhancement to the efficacy

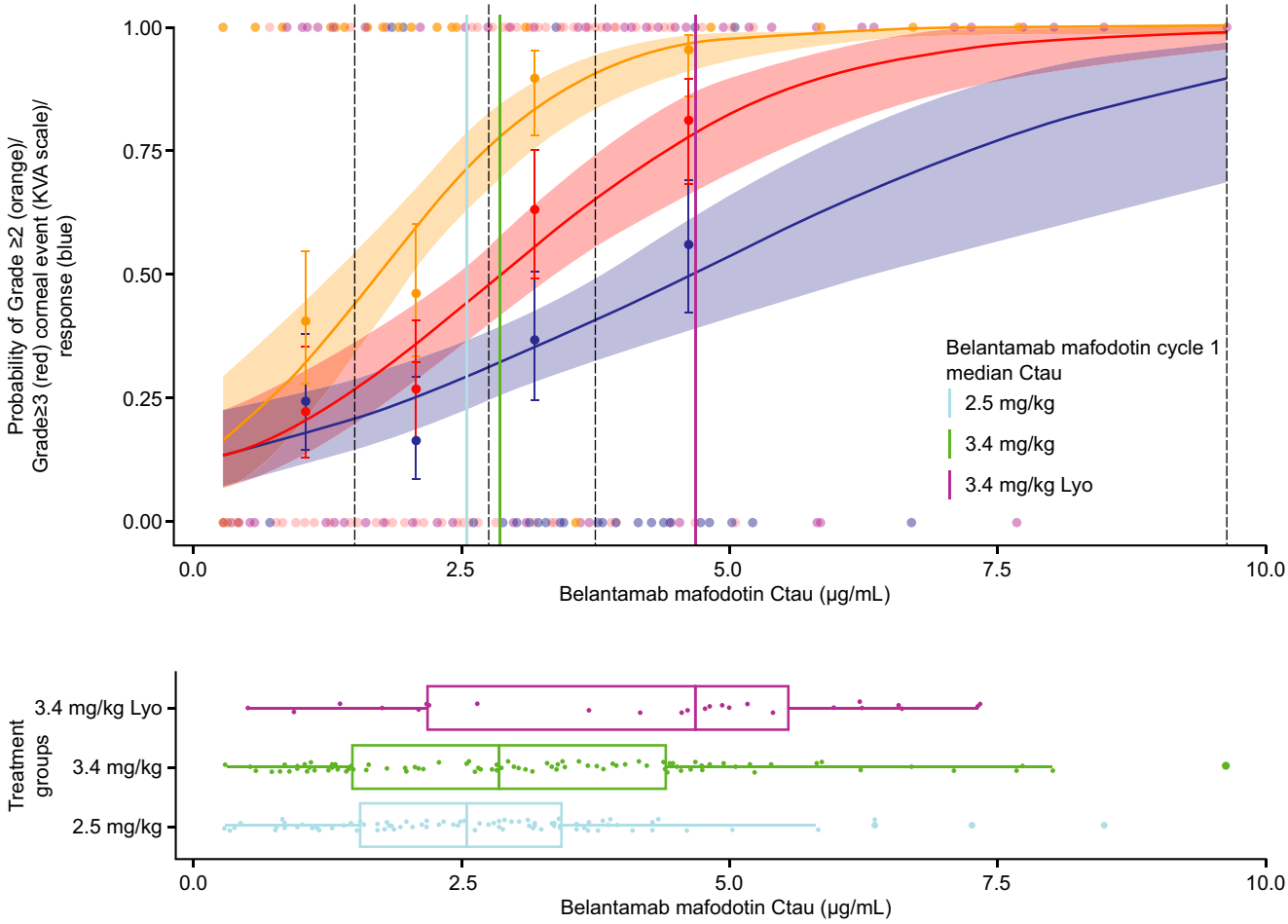

Figure 5 Integrated exposure–response analysis. Probability of grade ≥ 2 or grade ≥ 3 corneal event (KVA scale) and PoR by belantamab mafodotin C_{tau} (DREAMM-2 frozen liquid presentation), with accompanying boxplot of belantamab mafodotin C_{tau} by DREAMM-2 treatment group (frozen liquid and lyophilized presentations). C_{tau}, concentration at the end of the dosing interval (Day 21); KVA, keratopathy and visual acuity (KVA) scale; Lyo, lyophilized; PoR, probability of response.

of belantamab mafodotin is unknown. *In vitro*, afucosylation increased potency of effector cell-mediated antibody-dependent cellular cytotoxicity activity (by more than 1 log) compared with the nonenhanced homolog.[2] *In vivo*, the naked Fc-enhanced antibody (J6MO) slowed tumor growth, but had an inferior efficacy response compared with the Fc-enhanced ADC, which reduced tumor size but comparable *in vivo* data for a nonenhanced version of belantamab mafodotin are not available.[5] This needs to be considered if extrapolating findings discussed here to other ADCs.

The strengths of this work are that the models and analyses used a large body of data to enable assessment of covariates of clinical significance that affect belantamab mafodotin exposure and responses in patients with RRMM. This work also establishes relationships between belantamab mafodotin exposure and key efficacy and safety end points and the impact of disease burden. Limitations of the work include the evaluation of only one dosing schedule (Q3W) in the studies and the focus of the analysis on first cycle exposure and the first event of interest, without evaluation of the full time-course of exposure, dose modifications, and events. Development of an integrated PK/efficacy/safety time-course model could be useful for future belantamab mafodotin clinical development, such as for dose and schedule selection in combination treatments. Another limitation is that the relationship between exposure and sBCMA may have confounded the interpretation of the exposure–response analyses, as there was uncertainty whether (dose-dependent) exposure was driving the efficacy response or whether exposure was affected by disease burden or prognostic factors. These factors may be stronger drivers of the efficacy response than exposure within a certain clinically relevant dose range, and further investigation is warranted.

In conclusion, the exposure–response analyses of belantamab mafodotin 2.5 and 3.4 mg/kg found that both efficacy and safety end points were associated with disease factors and patient characteristics. Safety end points were more strongly associated with exposure than efficacy end points, particularly after disease factors and patient characteristics were accounted for in multivariate modeling. Overall, increases in belantamab mafodotin exposure increased the probability of corneal events (DREAMM-2, frozen liquid presentation), and cys-mcMMAF exposure increased the probability of thrombocytopenia (DREAMM-1 and DREAMM-2) without commensurate improvements in efficacy over the studied dose range. This supports the selection of the lower, 2.5 mg/kg dose of belantamab mafodotin for clinical use in RRMM.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

G.F.-B., C.R., J.C., H.S., S.V., and J.O. are employees of GlaxoSmithKline and hold ownership interests. R.C.J. is an employee of GlaxoSmithKline and holds ownership interests in GlaxoSmithKline and Novartis.

AUTHOR CONTRIBUTIONS

C.R., J.C., H.S., J.O., S.V., R.C.J., and G.F.-B. wrote the manuscript. C.R., R.C.J., S.V., J.O., and G.F.-B. designed the research. C.R., J.C., H.S., R.C.J., and G.F.-B. performed the research. C.R., J.C., H.S., R.C.J., S.V., and G.F.-B. analyzed the data.

DATA AVAILABILITY STATEMENT

Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

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