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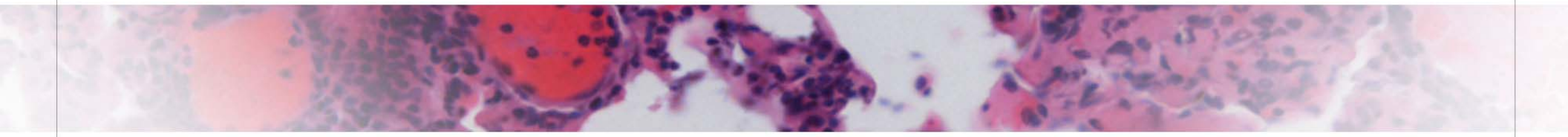

Exposure–Response (E–R) for Ocular Safety Endpoints for Belantamab Mafodotin (Belamaf), a B-Cell Maturation Antigen (BCMA)-Targeting Agent, in Patients with Relapsed/Refractory Multiple Myeloma (RRMM) in the DREAMM-2 Study

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Poster No. 1420

Background

Aims:

To assess the exposure–response relationships for ocular safety endpoints in the DREAMM-2 study

Belantamab mafodotin (belamaf; GSK2857916; BLENREP) is a first-in-class **ADC targeting BCMA**, approved in August 2020 by the US FDA and EMA for the treatment of patients with RRMM[1-3]

This **ADC** is comprised of a humanized afucosylated anti-BCMA monoclonal antibody linked to the microtubule-disrupting agent **MMAF** by a protease-resistant linker[1]

BCMA is a cell membrane receptor that is expressed on all malignant plasma cells and is essential for their proliferation and survival.[4] Belamaf binds to BCMA and eliminates MM cells by a **multimodal mechanism of action**, including delivery of MMAF into MM cells resulting in ADC-mediated apoptosis and release of markers characteristic of immunogenic cell death, and immune-dependent antibody-dependent cell-mediated cytotoxicity/phagocytosis (**Figure 1**)

The overall safety profile of belamaf is manageable and predominantly characterized by **ocular events** as anticipated for MMAF-containing ADCs. These were extensively characterized in the pivotal DREAMM-2 study[1]

Figure 1. Belamaf mode-of-action*

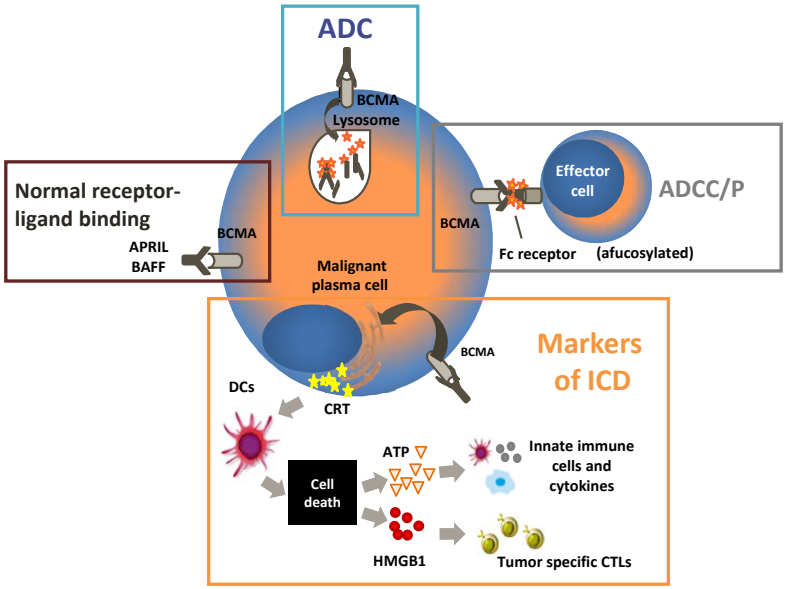


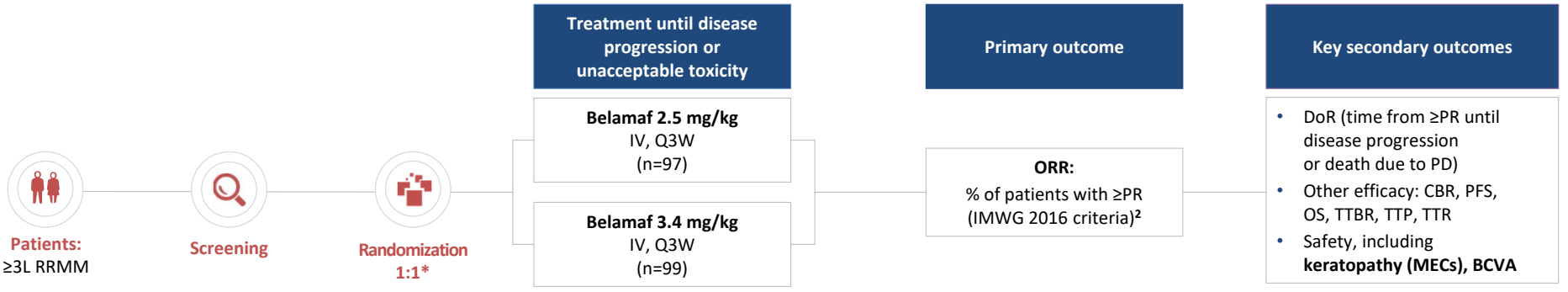
*Figure adapted from Richardson P, et al. Presented at the 61st Annual Meeting of the American Society of Hematology, December 7–10, 2019, Orlando, FL. Poster 1857.

ADC, antibody–drug conjugate; ADCC/P, antibody-dependent cell-mediated cytotoxicity/phagocytosis; APRIL, a proliferation-inducing ligand; ATP, adenosine triphosphate; BAFF, B-cell activating factor; BCMA, B-cell maturation antigen; CRT, calreticulin; CTLs, cytotoxic T-lymphocytes; DCs, dendritic cells; EMA, European Medicines Agency; Fc, fragment crystallizable; FDA, Food and Drug Administration; HMGB1, high mobility group box 1; ICD, immune cell death; MM, multiple myeloma; MMAF, monomethyl auristatin F; RRMM, relapsed/refractory multiple myeloma.

1. Lonial S, et al. *Lancet Oncol.* 2020;21:207–21; **2.** BLENREP Prescribing Information: GlaxoSmithKline plc; 2020; **3.** BLENREP SmPC. GSK plc; 2020; **4.** Tai YT, et al. *Immunotherapy.* 2015;7:1187–99.

Methods

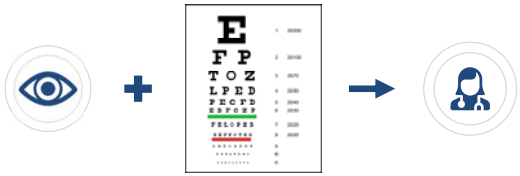
Figure 2. DREAMM-2 study design[1]



Ocular toxicity monitoring in the DREAMM-2 study**

- Patients had regular ocular examinations (at baseline, prior to each treatment cycle, or Q3W) by an eye care professional
- To fully characterize corneal events, a protocol-specified KVA scale was used, which focused on corneal exam findings (slit lamp examination identifying changes in the corneal epithelium, termed superficial punctate keratopathy [MECs; also reported as keratopathy AEs, with or without symptoms]) as well as changes in BCVA (measured by the Snellen Test)
- Patient-reported ocular symptoms (eg, blurred vision and dry eye) and keratopathy were reported as AEs and assessed by CTCAE criteria (v4.03)[3]

Ocular examinations in the DREAMM-2 study



Keratopathy (MECs)
Slit-lamp exam

BCVA
Snellen test

Graded on KVA scale

*Patients stratified based on number of previous lines of therapy (≤4 vs >4) and presence or absence of HR cytogenetic features; **Please check your local belamaf prescribing information for guidance on ocular toxicity monitoring.
AE, adverse event; BCVA, best-corrected visual acuity; CBR, clinical benefit rate; CTCAE, Common Terminology Criteria for Adverse Events; IMWG, International myeloma working group; KVA, keratopathy and visual acuity; MECs, microcyst-like epithelial changes; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression free survival; PR, partial response; Q3W, every 3 weeks; RRMM, relapsed/refractory multiple myeloma; TTBR, time to best response; TTP, time to progression; TTR, time to response.
1. Lonial S, et al. ASCO 2020. Poster 436; **2.** Kumar S, et.al. *Lancet Oncol*. 2016;17:e328-e46; **3.** National Cancer Institute. 2010. Available from: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf [Accessed Oct 13, 2020].

Methods

Methods – PopPK model used to generate individual patient exposure

- PopPK models were developed using NONMEM 7.3 software using the data from the DREAMM-1[1,2] and DREAMM-2[3] studies
- The PK of belamaf was characterized by a two-compartment model with linear elimination that slowed down over time
- Baseline patient characteristics and disease burden factors (soluble BCMA, IgG, and albumin) were found to significantly influence the PK of belamaf[4-6]
- Cycle 1 exposure values (e.g. **Cmax**, **Cavg**, and **Ctau**) were computed and used in the exposure–response analyses for DREAMM-2
- Moderate to high correlations were observed among these exposure values, with a wider range of values for Cavg and Ctau

Methods – data analyzed and endpoints

- N=194 patients received 2.5 (n=95) or 3.4 (n=99) mg/kg Q3W belamaf frozen liquid presentation[7]
- Probability of occurrence and timing of first **corneal event** (Grade ≥2 or ≥3, overall KVA scale grade)
- Probability of occurrence of an **eye-related adverse event** (Grade ≥1 or ≥2, CTCAE version 4.03, eg, keratopathy, blurred vision, dry eye)
- Probability of definite worsening in BCVA (≥0.3 change in LogMAR) in the better seeing eye
- Probability of unilateral or bilateral worsening in BCVA to 20/50 or worse (Snellen scale)

Methods – exposure–response modeling

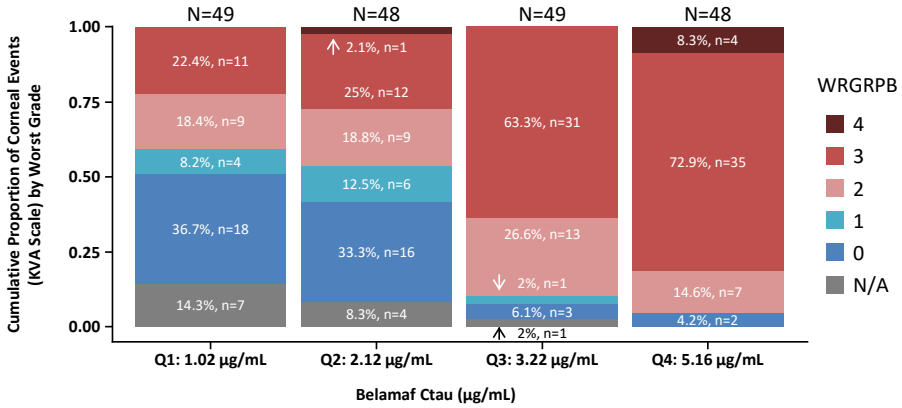
- Probability of occurrence of safety events was analyzed using **generalized linear models**
- Time-to-safety events were evaluated with **Kaplan-Meier** plots using quartile of exposure and covariates as well as via **Cox proportional hazard models** with baseline patient characteristics and Cycle 1 exposures as continuous variables
- **Covariates of Interest:** demographics (gender, race, age, weight), eye-related (history of dry eye, eye surgery, baseline keratopathy), and disease-related (ISS-stage, baseline sBCMA, IgG)
- Variables with the greatest improvement in objective function were selected step-by-step for inclusion in the full model ($p \leq 0.01$). A backward elimination process using a cutoff of $p \leq 0.001$ led to the final model
- R software was used for the exposure–response analyses

BCMA, B-cell maturation antigen; BCVA, best-corrected visual acuity; IgG, immunoglobulin G; Cmax, maximum concentration; Cavg, average concentration; Ctau, concentration at end of 3-week dosing interval; CTCAE, Common Terminology Criteria for Adverse Events; ISS, International Staging System; KVA, keratopathy and visual acuity; LogMAR, Logarithm of the Minimum Angle of Resolution; NONMEM, non-linear mixed-effect modelling; PopPK, population pharmacokinetics; Q3W, every 3 weeks.
1. Trudel S, et al. *Lancet Oncol*. 2018;19:1642; **2.** Trudel S, et al. *Blood Cancer J*. 2019;9:37; **3.** Lonial S, et al. *Lancet Oncol.* 2020;21:207; **4.** Ferron-Brady G, et al. AACR 2020. Poster CT196; **5.** Rathi C, et al. ACoP 2020 Poster. W-013; **6.** Collins J, et al. ACoP 2020 Poster 042; **7.** BLENREP US PI: GlaxoSmtihKline plc; 2020.

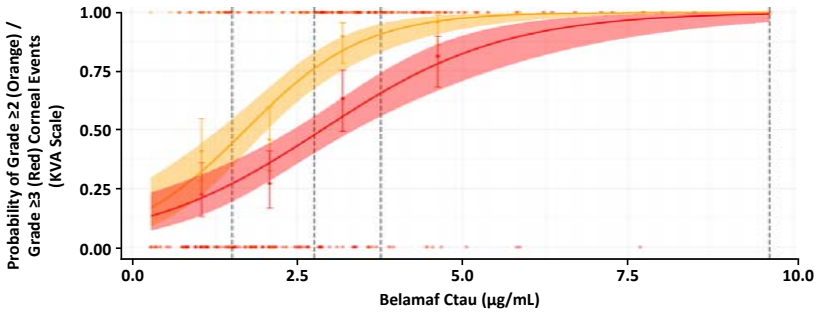
Results

Figure 3. Exposure–response for corneal events (KVA Scale)

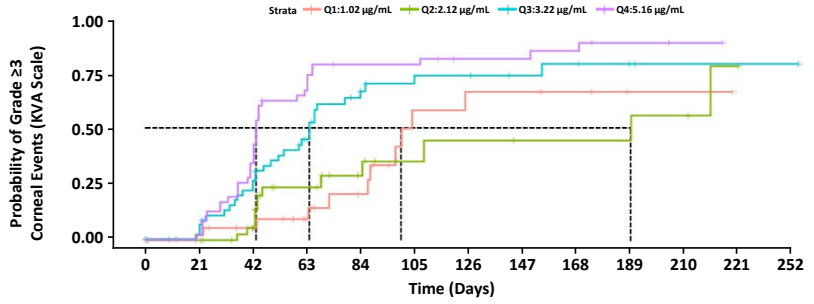
A. Proportion of corneal events by Grade and quartile of Ctau



B. Probability of corneal events (KVA scale)



C. Time to first Grade ≥3 corneal event (KVA scale)



Exposure–response – corneal events

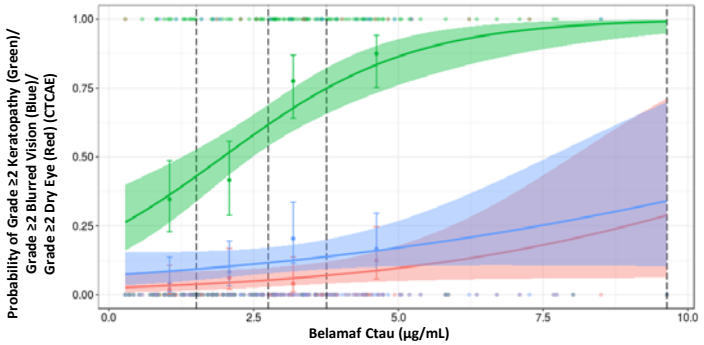
- Higher probability and higher grade of corneal events were seen with higher belamaf Ctau (**Figure 3A**)
- **Higher belamaf Ctau** was associated with higher probability of **Grade ≥2 or ≥3 corneal events** (**Figure 3B**) and was **inversely correlated with time to first Grade ≥3 corneal event** (**Figure 3C**)
- Higher **baseline sBCMA** was associated with lower probability of these events
- **History of dry eye** was associated with higher probability of Grade ≥2 corneal events

Ctau, concentration at end of 3-week dosing interval; KVA, keratopathy and visual acuity; sBCMA, soluble B-cell maturation antigen; WRGRPB, worst grade post baseline.

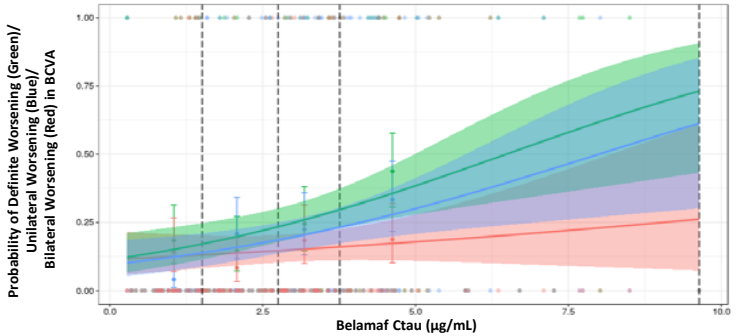
Results

Figure 4. Exposure–response for eye-related events (CTCAE, LogMAR, Snellen)

A. Probability of ocular AE (CTCAE)



B. Probability of changes in BCVA



Exposure–Response – ocular AE

- **Higher belamaf Ctau** was associated with probability of any Grade or Grade ≥2 **keratopathy**
- Probability of **dry eye** or **blurred vision** reported by the patient was not associated with belamaf exposure
- **History of dry eye** was associated with probability of any grade of blurred vision
- **Presence of keratopathy at baseline** was associated with probability of Grade ≥2 blurred vision and earlier occurrence of blurred vision of any Grade or Grade ≥2
- Higher **baseline sBCMA** was associated with lower probability of any grade of blurred vision, and any Grade or Grade ≥2 keratopathy

Exposure–response – changes in BCVA

- Belamaf exposure was associated with some BCVA endpoints when evaluated on its own. It was no longer significant after inclusion of sBCMA, the most significant covariate. Lower sBCMA is associated with higher belamaf exposure and higher probability of response[1,2]
- Probability of **definite worsening in BCVA** or **unilateral worsening in BCVA to 20/50 or worse** was not associated with belamaf exposure but was inversely related to baseline sBCMA
- Probability of **bilateral worsening in BCVA to 20/50 or worse** was only found to be higher in female patients

AE, adverse event; BCVA, best corrected visual acuity; Ctau, concentration at end of 3-week dosing interval; CTCAE, Common Terminology Criteria for Adverse Events; KVA, keratopathy and visual acuity; LogMAR, Logarithm of the Minimum Angle of Resolution; sBCMA, soluble B-cell maturation antigen.

1. Ferron-Brady G, et al. AACR Meeting 2020 Poster CT196; **2.** Rathi C, et al. ACoP 2020 Poster W-013.

Conclusions

In the integrated exposure–response safety analyses of DREAMM-2, after accounting for patient and disease factors, we found that:

- Higher belamaf exposure (Ctau) was associated with an increased probability of corneal events and keratopathy AEs, as well as with an earlier occurrence of these events
- Occurrence of blurred vision and dry eye reported by the patient were not found to be associated with belamaf exposure
- When the inverse association with baseline sBCMA was included, the probability and timing of worsening in visual acuity was not associated with belamaf exposure
- History of dry eye was associated with probability of corneal events and blurred vision
- Further analyses of the pivotal DREAMM-2 study of single-agent belamaf are presented at this meeting (posters 1417, 1419, 2278, 3221, 3224, and 3248)
- Further exploration of the pharmacokinetics and ocular toxicity relationship is ongoing in other DREAMM studies; different dosing regimens are being actively explored[1]

AE, adverse event; Ctau, concentration at end of 3-week dosing interval; KVA, keratopathy and visual acuity; sBCMA, soluble B-cell maturation antigen.

1. Popat R, et al. ASH 2020 Poster 1419.

Disclosures and Acknowledgments

GFB, **CR**, **JC**, **HS**, **JO,** and **RCJ** are employees of GSK and hold stocks/shares. **RCJ** also holds stocks/shares in Novartis

These data were previously presented in part at the American Association of Cancer Research (AACR) Meeting (virtual format) 2020 (Ferron-Brady G, et al. AACR 2020. Poster CT196) and the American Conference of Pharmacometrics (ACoP), virtual format (Rathi C, et al. ACoP 2020. Poster W-013)

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