Relationship between corneal exam findings, best-corrected visual acuity (BCVA), and ocular symptoms in patients with relapsed or refractory multiple myeloma (RRMM) receiving belantamab mafodotin (belamaf)

E. TERPOS[1], A. BADROS[2], R. POPAT[3], P. RODRIGUEZ-OTERO[4], A. FAROOQ[5], B. JENG[2], S. DEGLI ESPOSTI[6], V. JADHAV[7], E. LEWIS[8], I. GUPTA[9], J. OPALINSKA[9], A. PALUMBO[10], S. TRUDEL[11] | [1]National and Kapodistrian University of Athens School of Medicine, Athens, Greece; [2]University of Maryland School of Medicine, Baltimore, MD, USA; [3]University College London Hospitals, NHS Foundation Trust, London, UK; [4]Clinica Universidad de Navarra, Instituto de Investigación Sanitaria de Navarra, Navarra, Spain; [5]University of Chicago Medical Center, Chicago, IL, USA; [6]NIHR Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, UK; [7]GlaxoSmithKline, Bengaluru, India; [8]GlaxoSmithKline, Research Triangle Park, NC, USA; [9]GlaxoSmithKline, Upper Providence, PA, USA; [10]GlaxoSmithKline, Zug, Switzerland; [11]Princess Margaret Cancer Centre, Toronto, ON, Canada

BACKGROUND

Belantamab mafodotin (GSK2857916; belamaf; BLENREP) is a B-cell maturation antigen (BCMA)-targeting antibody-drug conjugate.[1]

Belamaf is approved in the US and EU as a monotherapy for the treatment of adult patients with RRMM.[2]

The anti-myeloma activity of single-agent belamaf was established in a phase 2 trial in patients with RRMM: the DREAMM-2 trial (NCT03525678).[3]

Ocular events are a known effect of mafodotin[4] and have occurred in patients treated with belamaf.[3,5]

Ocular events with belamaf reported by eye care professionals and patients in the pivotal DREAMM-2 trial included:

- Keratopathy (including superficial punctate keratopathy and/or microcyst-like epithelial changes)[3,5]
- BCVA changes[5] and ocular symptoms, such as blurred vision and dry eye[3,5]
- Such events were documented as having resolved in the majority of patients.[5]

Dose reductions or delays based on corneal exam findings and BCVA changes are being used to manage belamaf-related corneal changes and other ocular events but require referral to an eye care professional.[5]

AIM

Investigate the relationships between corneal exam findings, BCVA changes, and patient-reported ocular symptoms to explore if BCVA changes and symptoms could guide dosing, rather than corneal exams.

METHODS

This was a *post hoc* analysis of data from the DREAMM-2 trial, an open-label, two-arm, phase 2 study in patients ≥18 years with RRMM with disease progression after ≥3 lines of therapy. Patients were refractory to previous therapy with immunomodulatory drugs and proteasome inhibitors, and refractory or intolerant to an anti-CD38 monoclonal antibody.[3]

Eye evaluations were performed by eye care professionals on all patients at baseline and prior to each dose of single-agent belamaf (2.5 mg/kg), and included:

- BCVA assessment using Snellen chart and manifest refraction
- Corneal exam using slit lamp microscopy.

Ocular adverse events (AEs) were graded based on corneal exam findings and change in BCVA from baseline:

- Assessment of grade (GR) was based on the worst finding in the worse eye.

Patient-reported ocular symptoms, as per Common Terminology Criteria for Adverse Events (CTCAE), and ocular symptoms and vision-related functioning, as per Ocular Surface Disease Index (OSDI*), were used to evaluate the impact of treatment-related ocular toxicity.

For this *post hoc* analysis, concordance† and discordance were defined according to different levels of severity:

- Keratopathy: GR 0–2 (none to moderate) vs GR 3–4 (severe)
- BCVA: GR 0–1 (none or mild) vs GR 2–4 (moderate to severe)
- Patient-reported ocular symptoms as per CTCAE: presence of symptoms vs absence of symptoms
- OSDI*: OSDI positive (at least one AE reported most of the time) vs OSDI negative (no AE reported most of the time).

*Questions 1–9 ≥ most of the time on any of the items were used to represent an ocular-related event that may be associated with treatment; response scale ('All of the time' to 'None of the time').

†Cohen's kappa coefficient (κ) was calculated to measure inter-rater agreement, where 0.01-0.20 slight; 0.21-0.40 fair; 0.41-0.60 moderate; 0.61-0.80 substantial; 0.81-1.00 almost perfect.[6]

RESULTS

Results are reported for 95 patients treated with 2.5 mg/kg belamaf.

Corneal Exam Findings, BCVA, and CTCAE-Reported Ocular Symptoms

In 12.5% of eye evaluations, GR 3–4 keratopathy was associated with minimal or no (GR 0–1) BCVA changes (**Table 1**).

The highest frequency of corneal exam findings in evaluations with GR 3–4 keratopathy and GR 0–1 BCVA included severe keratopathy (24%) and diffuse microcyst-like epithelial changes (70%) (**Table 2**).

RESULTS (CONTINUED)

When patient-reported ocular symptoms per CTCAE were also considered, only 7.5% of evaluations found GR 3–4 keratopathy with GR 0–1 BCVA changes and no symptoms (**Table 3**).

The highest frequency of corneal exam findings in evaluations with GR 3–4 keratopathy and GR 0–1 BCVA plus no symptoms included severe keratopathy (24%) and diffuse microcyst-like epithelial changes (69%) (**Table 4**).

Table 1: Summary of Concordance and Discordance Between Corneal Exam Findings and BCVA Changes

Keratopathy and BCVA Changes* Only (Total Evaluations, N = 773)	Events, n (%)
GR 0–2 Keratopathy and GR 0–1 BCVA	460 (59.5)
GR 3–4 Keratopathy and GR 2–4 BCVA	96 (12.4)
GR 0–2 Keratopathy and GR 2–4 BCVA	120 (15.5)
GR 3–4 Keratopathy and GR 0–1 BCVA	97 (12.5)

*κ = 0.2794

Table 2: Summary of Corneal Exam Findings in Evaluations with GR 3–4 Keratopathy and GR 0–1 BCVA

Corneal Exam Findings	Evaluations with GR 3–4 Keratopathy and GR 0–1 BCVA (n = 97)
Severe keratopathy*, n (%)	23 (24)
Diffuse microcyst-like epithelial changes, n (%)	68 (70)
Diffuse epithelial or stromal edema, n (%)	7 (7)
Sub-epithelial haze (central), n (%)	7 (7)
Active stromal opacity (central), n (%)	1 (1)
Corneal ulcer, n (%)	1 (1)

*Severe superficial keratopathy with or without diffuse microcyst-like deposits involving the central cornea, sub-epithelial haze (central), or a new central stromal opacity.[5]

Table 3: Summary of Concordance and Discordance Between Corneal Exam Findings and BCVA Changes/CTCAE-Reported Ocular Symptoms

Keratopathy and BCVA Changes/Ocular Symptoms* (Total Evaluations, N = 773)	Events, n (%)
GR 0–2 Keratopathy and (GR 0–1 BCVA and no symptoms)	300 (38.8)
GR 3–4 Keratopathy and (GR 2–4 BCVA, or symptoms)	135 (17.4)
GR 0–2 Keratopathy and (GR 2–4 BCVA, or symptoms)	280 (36.2)
GR 3–4 Keratopathy and (GR 0–1 BCVA and no symptoms)	58 (7.5)

*κ = 0.1566

Table 4: Summary of Corneal Exam Findings in Evaluations with GR 3–4 Keratopathy and GR 0–1 BCVA plus No Symptoms

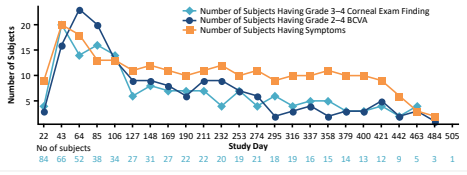
Corneal Exam Findings	Evaluations with GR 3–4 Keratopathy and GR 0–1 BCVA plus No Symptoms (n = 58)
Severe keratopathy*, n (%)	14 (24)
Diffuse microcyst-like epithelial changes, n (%)	40 (69)
Diffuse epithelial or stromal edema, n (%)	5 (9)
Sub-epithelial haze (central), n (%)	5 (9)
Active stromal opacity (central), n (%)	1 (2)
Corneal ulcer, n (%)	0

*Severe superficial keratopathy with or without diffuse microcyst-like deposits involving the central cornea, sub-epithelial haze (central), or a new central stromal opacity.[5]

Corneal Exam Findings, BCVA, and CTCAE-Reported Ocular Symptoms over Time

GR 3–4 keratopathy, GR 2–4 BCVA, and CTCAE-reported ocular symptoms were found in approximately 20 patients within about 64 days of belamaf treatment. The number of patients with GR 3–4 keratopathy or GR 2–4 BCVA diminished over time, whereas a higher number of patients with symptoms plateaued before diminishing. This suggests ocular symptoms may persist even with a decrease in GR 3–4 keratopathy or GR 2–4 BCVA (**Figure 1**).

Figure 1: Number of Patients with GR 3–4 Keratopathy, GR 2–4 BCVA, and CTCAE-Reported Ocular Symptoms over Time



CTCAE-Reported Ocular Symptoms

The two most frequent CTCAE-reported ocular symptoms in all evaluations were blurred vision (n = 172) and dry eye (n = 90) (**Table 5**).

Of those evaluations with blurred vision, 42/172 (24%) were GR 3–4 keratopathy and 130/172 (76%) were GR 0–2 keratopathy. Of those evaluations with dry eye, 18/90 (20%) were GR 3–4 keratopathy and 72/90 (80%) were GR 0–2 keratopathy (**Table 5**).

Table 5: Summary of CTCAE-Reported Ocular Symptoms Detected in All Evaluations, Evaluations with GR 3–4 Keratopathy, and Evaluations with GR 0–2 Keratopathy

Ocular Symptoms (Preferred Term)	All Evaluations (N = 773)	Evaluations with GR 3–4 Keratopathy (n = 193)	Evaluations with GR 0–2 Keratopathy (n = 580)
Any event, n (%)	302 (39)	87 (45)	215 (37)
Vision blurred, n (%)	172 (22)	42 (22)	130 (22)
Dry eye, n (%)	90 (12)	18 (9)	72 (12)
Ocular discomfort, n (%)	33 (4)	12 (6)	21 (4)
Eye irritation, n (%)	29 (4)	4 (2)	25 (4)
Photophobia, n (%)	29 (4)	16 (8)	13 (2)
Diplopia, n (%)	20 (3)	4 (2)	16 (3)
Visual acuity reduced, n (%)	16 (2)	2 (1)	14 (2)
Visual impairment, n (%)	13 (2)	1 (<1)	12 (2)
Eye pain, n (%)	2 (<1)	0	2 (<1)
Eye pruritus, n (%)	1 (<1)	0	1 (<1)
Ocular hyperaemia, n (%)	1 (<1)	0	1 (<1)

OSDI

In only 5% of evaluations, GR 3–4 keratopathy was not associated with having an OSDI symptom or impact that was ≥ most of the time (**Table 6**).

When patients reported an ocular symptom on the OSDI that was ≥ most of the time or when that symptom occurred with GR 3–4 keratopathy or GR 0–2 keratopathy, the most frequent CTCAE-reported ocular symptoms were blurred vision (22%, 21%, and 23%, respectively) and dry eye (11%, 14%, and 10%, respectively) (**Table 7**).

Table 6: Summary of Concordance and Discordance for OSDI: 'Most of the Time' Analysis

Keratopathy and OSDI* (Total Evaluations, N = 773)	Events, n (%)
GR 0–2 Keratopathy and OSDI No Item Most of the Time	236 (31)
GR 3–4 Keratopathy and OSDI At Least One Item† ≥ Most of the Time	97 (13)
GR 0–2 Keratopathy and OSDI At Least One Item† ≥ Most of the Time	184 (24)
GR 3–4 Keratopathy and OSDI No Item Most of the Time	40 (5)
Missing Values	216 (28)

*κ = 0.1993; †OSDI Questions 1–9 only. Items 1–5 address the frequency of the following eye-related problems during the course of the prior week (Range: 'All of the time' to 'None of the time'): eyes that are sensitive to light; eyes that feel gritty; painful or sore eyes; blurred vision; and poor vision. Items 6–9 address the frequency of eye-related problems that limit performing the following tasks during the prior week: reading; driving at night; working with a computer or bank machine (ATM); and watching TV. All responses range from 'All of the time' to 'None of the time'.

Table 7: Summary of CTCAE-Reported Ocular Symptoms Detected in Evaluations with OSDI Positive*, Evaluations with OSDI Positive* plus GR 3–4 Keratopathy, and Evaluations with OSDI Positive* plus GR 0–2 Keratopathy

Ocular Symptoms (Preferred Term)	Evaluations with OSDI Positive (n = 281)	Evaluations with OSDI Positive and GR 3–4 Keratopathy (n = 97)	Evaluations with OSDI Positive and GR 0–2 Keratopathy (n = 184)
Any event	135 (48)	51 (53)	84 (46)
Vision blurred, n (%)	63 (22)	20 (21)	43 (23)
Dry eye, n (%)	32 (11)	14 (14)	18 (10)
Ocular discomfort, n (%)	19 (7)	3 (3)	16 (9)
Photophobia, n (%)	16 (6)	13 (13)	3 (2)
Eye irritation, n (%)	15 (5)	3 (3)	12 (7)
Visual acuity reduced, n (%)	10 (4)	2 (2)	8 (4)
Diplopia, n (%)	6 (2)	2 (2)	4 (2)
Visual impairment, n (%)	5 (2)	1 (1)	4 (2)
Eye pain, n (%)	1 (<1)	0	1 (<1)
Eye pruritus, n (%)	1 (<1)	0	1 (<1)

*OSDI Questions 1–9 only.

CONCLUSIONS

In evaluations with no/mild (≤GR 1) BCVA changes and no ocular symptoms, GR 3-4 keratopathy was rarely observed (only 7.5% of the time [58/773]).

In evaluations where frequent (≥ most of the time) ocular symptoms were not reported (based on OSDI questionnaire questions 1-9), GR 3-4 keratopathy was rarely observed (only 5% of the time).

These results suggest that to determine dose modifications and patient management:

- BCVA and CTCAE-reported ocular symptoms should be further investigated to determine whether they may represent surrogates of corneal alterations.
- The OSDI questionnaire, which asks patients to report their ocular symptoms and vision-related functioning, should be further investigated to determine whether it can become a surrogate for corneal alterations.

DISCLOSURES

ET has received consulting fees from Amgen, Celgene, Genesis Pharmaceuticals, Janssen, Sanofi, and Takeda; research funding from Amgen, Genesis Pharmaceuticals, Janssen, Sanofi, and Takeda; and honoraria from Amgen, Bristol-Myers Squibb, Celgene, Genesis Pharmaceuticals, Janssen, Novartis, Sanofi, and Takeda. **AB** has received consulting fees from Amgen. **RP** has received consulting fees from AbbVie, Celgene, GlaxoSmithKline, and Takeda; research funding from Celgene; and honoraria and personal fees from GlaxoSmithKline, Janssen, and Takeda. **PRO** has received consulting fees from Takeda; and consulting fees and honoraria from AbbVie, Amgen, Celgene, GlaxoSmithKline, Janssen, Kite Pharma, Oncopeptides, and Sanofi. **AF** has received consulting fees from GlaxoSmithKline. **BJ** has received consulting fees from GlaxoSmithKline, Kedrion, and Merck; and has stocks/shares in EyeGate. **SDE** has received consulting fees and honoraria from GlaxoSmithKline. **VJ, EL, JO**, and **AP** are employees of and have stocks/shares in GlaxoSmithKline. **IG** is an employee of and has stocks/shares in GlaxoSmithKline, and Novartis. **ST** has received consulting fees from Amgen, Celgene, and GlaxoSmithKline; research funding from Amgen, Celgene, Genentech, GlaxoSmithKline, and Janssen; and honoraria from Amgen, Celgene, Janssen, Karyopharm, Sanofi, and Takeda.

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CONTACT INFORMATION

Evangelos Terpos, eterpos@med.uoa.gr