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DREAMM-2 (NCT03525678): Single-Agent Belantamab Mafodotin (Belamaf) Effects on Patient-Reported Outcome (PRO) Measures in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)

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Background

In the heavily pre-treated RRMM patient population, extending survival while maintaining HRQoL is an important treatment goal.[1]

Typically, these patients have poor HRQoL; maintenance of, rather than improvement in, HRQoL has been reported as a benefit of commonly used treatments.[1]

Belantamab mafodotin (belamaf; BLENREP) is a first-in-class BCMA-binding, humanized, afucosylated, monoclonal MMAF-containing ADC with a multi-modal MoA.[2,3]

In the pivotal DREAMM-2 study (NCT03525678), single-agent belamaf demonstrated clinically meaningful and durable responses in patients with heavily pre-treated RRMM, and had a manageable safety profile.[4,5]

Ocular events are commonly reported with MMAF-containing ADCs, such as belamaf.[6]

The most frequent ocular symptoms associated with belamaf treatment are dry eye, blurred vision or a decline in BCVA.[7]

- In DREAMM-2, ocular events including keratopathy (MECs, an eye examination finding with/ without symptoms), change in BCVA, or symptoms (blurred vision and dry eye) were the most common AEs reported during belamaf treatment.[5,6] No patients treated with belamaf to date have had permanent vision loss.[7]

MECs led to dose delays in 47% of patients in the 2.5 mg/kg arm, however most events improved, and responses to belamaf were durable despite dose modifications.[8]

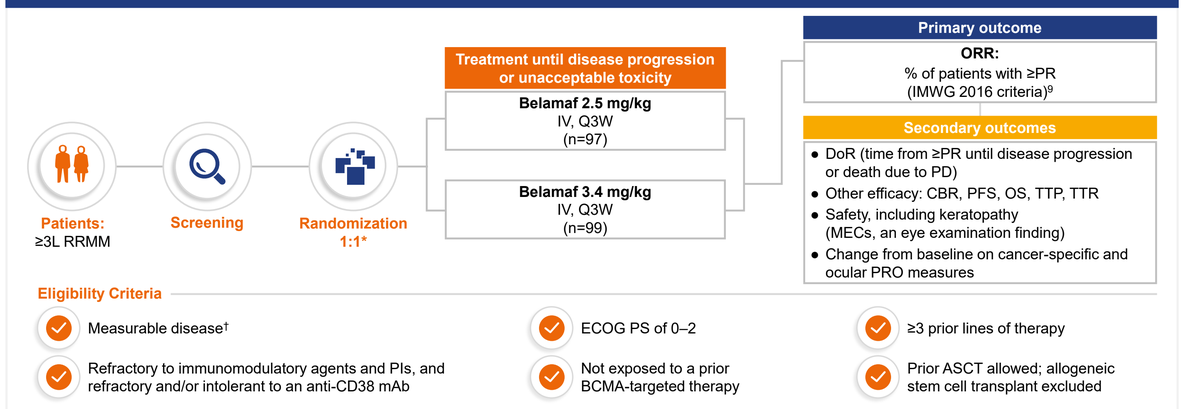
DREAMM-2 included PROs to assess HRQoL and ocular symptoms and vision-related function.

Aims

To understand the impact of single-agent belamaf at 2.5 mg/kg Q3W (the approved dose) on disease and treatment-related symptoms, functioning, and HRQoL in the DREAMM-2 study.

Methods

Figure 1. DREAMM-2 study design[4]



*Patients stratified based on number of previous lines of therapy (≤4 vs. >4) and presence or absence of HR cytogenetic features; †defined as serum myeloma protein (M-protein) ≥0.5 g/dL; urine M-protein ≥200 mg/24 h; serum FLC assay: involved FLC level ≥10 mg/dL and an abnormal serum FLC ratio (<0.26 or >1.65).

Collection of PROs in DREAMM-2

PROs are included as secondary outcomes in the ongoing DREAMM-2 study of single-agent belamaf (**Table 1**).

Data on cancer- and treatment-related symptoms and impacts were collected as shown in the table.[10, 11]

Patients used a tablet to complete PRO surveys electronically, ahead of clinical discussions at study visits.[10]

Group-level mean changes were evaluated over the course of the study.[10]

For EORTC-CLC-C30 and EORTC-MY20, we evaluated within-patient change across cancer-specific measures based on a **10-point** threshold for improvement.[12]

For OSDI, within-patient changes in vision-related function were based on thresholds of **≥12.5**[10] **and 16.67 points**.

- Threshold based on an analysis that used recommended methods for establishing clinically meaningful change thresholds for ocular PROs that measure treatment-related corneal events in patients with RRMM receiving belamaf.

Table 1. Collection of HRQoL and MM-related symptom data in DREAMM-2[10, 11]

Instrument	Domains/purpose	Schedule
Global HRQoL measures		
EORTC-QLQ-C30	Multiple symptom and functioning domains, including pain, fatigue, and overall health status/QoL	Baseline and every 6 weeks
Disease symptom measures		
EORTC-QLQ-MY20	Disease symptoms, future perspective, body image, side effects	Baseline and every 6 weeks
Vision-related measures		
OSDI	Ocular symptoms, vision-related function, and environmental triggers related to dry eye	Baseline and every 3 weeks
NEI-VFQ-25	Ocular-related QoL and functioning	

Results

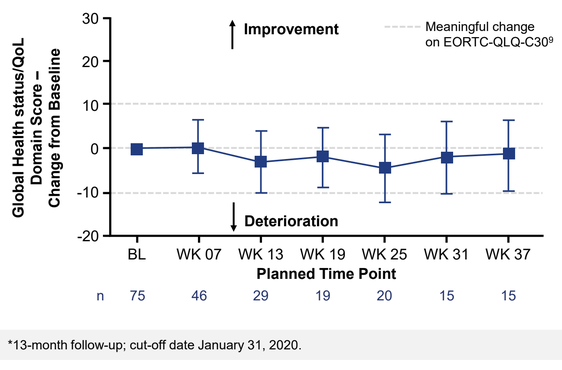
Global and MM-related HRQoL: EORTC-QLQ-C30 and EORTC-QLQ-MY20

Global health status/QoL remained relatively stable over time (**Figure 2**).

>25% of patients had meaningful within-patient improvements in physical functioning and disease symptoms by Week 7 (6-month follow-up; **Table 2**).

>30% of patients had meaningful within-patient improvements in fatigue at Weeks 19 and 25 (6-month follow-up).

Figure 2. EORTC-QLQ-C30 Global Health Status/QoL[9]*



*13-month follow-up; cut-off date January 31, 2020.

Table 2. Patients with ≥10-point improvement[11] from baseline in EORTC-QLQ-C30 and EORTC-QLQ-MY20[10]*

	Week	Patients n/N (%)	Week	Patients n/N (%)
EORTC-QLQ-C30 Domain				
Fatigue	7 13	21/46 (46) 12/29 (41)	19 25	6/19 (32) 6/19 (32)
Physical Functioning	7 13	13/46 (28) 8/29 (28)	19 25	3/19 (16) 4/19 (21)
Pain	7 13	14/46 (30) 9/29 (31)	19 25	4/19 (21) 3/19 (16)
EORTC-QLQ-MY20 Domain				
Disease Symptoms (pain in different locations)	7 13	17/45 (38) 8/28 (29)	19 25	5/18 (28) 6/18 (33)

*6-month follow-up; cut-off date June 21, 2019. Note that numbers of patients decline over time as fewer patients completed PRO questionnaires at later visits, and these numbers represent the number calculated among patients still enrolled at the respective time point.

Vision-Related Function: OSDI

49.5% and 44.2% of patients reported a change on the OSDI vision-related function (VRF) sub-scale of 12.5 and 16.67 points, respectively, which is generally in line with eye care professional examination findings (**Table 3**).

Patient-reported VRF reduction occurred at around the same time as symptom onset and shortly after eye examination findings.

A high proportion of patients recovered from their VRF reduction, similar to outcomes with eye examination findings and symptoms.

- It is not possible to assess recovery in all cases as some patients remain on treatment/in follow up, and some were lost to follow up, see 'Recovery of ocular events with longer term follow-up in the DREMM-2 study' Lonial et al. COMy 2021.

Median time to improvement from a worst-case score on the OSDI VRF domain was 24 and 45 days with the 12.5 and 16.67 thresholds, respectively.

EORTC-QLQ-C30 changes in patients with reduction in OSDI vision-related function

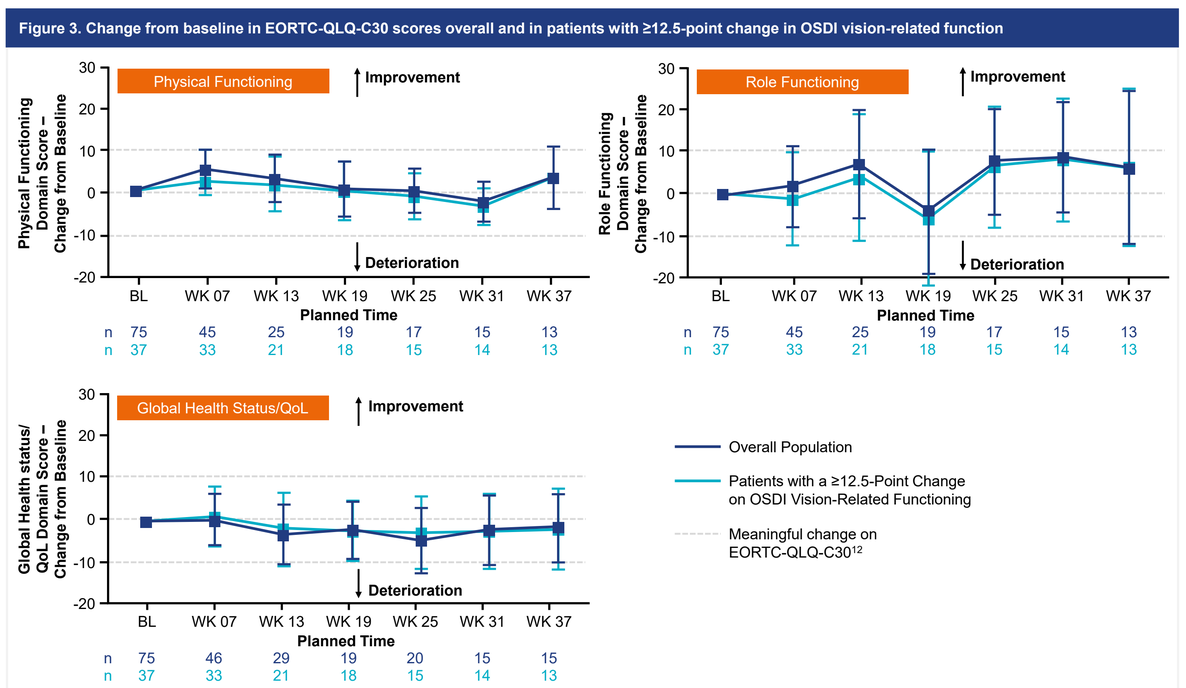
There was no change in overall patient-reported Global Health Status/QoL, Physical Functioning, or Role Functioning domain scores of the EORTC-QLQ-C30, even among patients with a minimal meaningful within-patient reduction in VRF by OSDI (**Figure 3**).

Table 3. Patient-reported vision-related function and ocular examination findings

Scale	OSDI		KVA		
Measure	**Patient-reported Visual Function Sub-scale**		**Eye Care Professional Examination Finding**		
	≥12.5-point worsening from baseline (n=95)	**≥16.67-point worsening from baseline (n=95)**	**Keratopathy (MECs) (n=95)**	**BCVA change (n=95)**	**Keratopathy (MECs) + BCVA change (n=95)**
Patients with event, n (%)	47 (49.5)	42 (44.2)	Any Grade: 68 (72) *Grade 1: 8 (8)* *Grade 2: 16 (17)* *Grade 3: 43 (45)* *Grade 4: 1 (1)*	Any Grade: 51 (54) *Grade 1: 7 (7)* *Grade 2: 15 (16)* *Grade 3: 28 (29)* *Grade 4: 1 (1)*	Any Grade: 68 (72) *Grade 1: 7 (7)* *Grade 2: 14 (15)* *Grade 3: 45 (47)* *Grade 4: 2 (2)*
Time to onset of first occurrence, days median (range)	44 (21–231)	60.7 (21–231)	37.0 (19–143)	64.0 (20–213)	36.0 (19–143)
Duration of first event, days median (range)	24[6] (7–350)	45.1 (9–350)	86.5 (8–358)	33.0 (8–127)	96.0 (8–358)
Event outcomes, n/N (%)					
Recovered	34/47 (72)*	32/42 (76)*	46/60 (77)†	34/44 (77)†	45/61 (74)†
Not recovered	13/47 (28)	10/42 (24)	14/60 (23)	10/44 (23)	16/61 (26)

13-month follow-up; cut-off date January 31, 2020. *Recovery defined as ≥12.5-point improvement. †Recovery of keratopathy (MECs) was defined as an event that was deemed clinically stable by the eye care professional. Clinical stability was defined as any Grade 1 exam finding (per KVA scale) or no exam finding, and either a one-line decline in vision or no change in vision when compared with baseline.

Figure 3. Change from baseline in EORTC-QLQ-C30 scores overall and in patients with ≥12.5-point change in OSDI vision-related function



13-month follow-up; cut-off date January 31, 2020.

NEI-VFQ-25 Item Scores: Impact on driving and recovery as assessed by NEI-VFQ-25

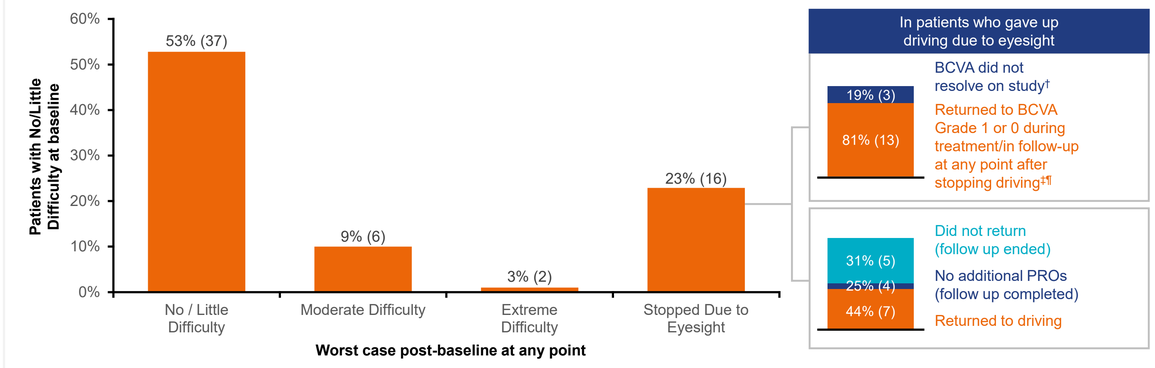
At the beginning of the study, 74% (70) patients reported having No Difficulty or A Little Difficulty with driving.

Of these patients, 53% (37) stated that they were able to drive with No Difficulty or A Little Difficulty while on treatment (**Figure 4**).

At worst case post-baseline, 9% (6) had Moderate Difficulty with driving during the daytime, 3% (2) had Extreme Difficulty, and 23% (16) Stopped Driving Due to Eyesight.

In the 23% (16) patients who Stopped Driving Due to Eyesight, time to onset of first occurrence was a median of 63.5 days. Of these patients that stopped driving, 81% (13) returned to a BCVA of Grade 0 or 1 later during treatment/follow up, with 44% (7) returning to driving on-study (patients may have experienced Grade ≥2 BCVA events after recovery of the first event; one patient did not have Grade ≥2 BCVA events before or after stopping driving). Of the 56% (9) patients who did not return to driving, 44% (4) did not have a follow-up PRO assessment.

Figure 4. Worse case post-baseline shift in driving among patients with No Difficulty or A Little Difficulty at baseline (N=70)*



13-month follow-up; cut-off date January 31, 2020. BCVA recovery based on routine study-mandated ophthalmic exam.
*Three patients (4%) with no/little difficulty in visual functioning at baseline stopped driving due to reasons not related to visual functioning change. Post-baseline assessments were missing for 6 patients (9%). †For 2 patients who did not return to Grade 0 or 1 BCVA post stopping driving, follow-up ended due to death or end of treatment. ‡Patients may have experienced Grade ≥2 BCVA events after recovery of the first event. ¶One patient did not have Grade ≥2 BCVA events before or after stopping driving.

NEI-VFQ-25 Item Scores: Impact on reading and recovery as assessed by NEI-VFQ-25

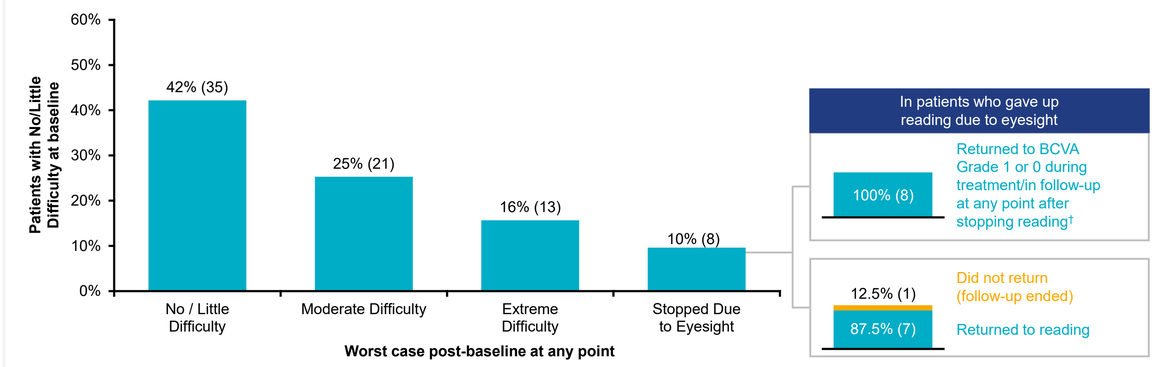
At the beginning of the study, 87% (83) patients reported having No Difficulty or A Little Difficulty reading.

Of these patients, 42% (35) stated that they were able to read ordinary print with No Difficulty or A Little Difficulty throughout the study **(Figure 5)**.

At worst case post-baseline, 25% (21) had Moderate Difficulty reading ordinary print, 16% (13) had Extreme Difficulty, and 10% (8) Stopped Reading Due to Eyesight.

Time to first occurrence of Stopped Reading Due to Eyesight was a median of 85 days. Of the 8 patients who stopped reading, 100% (8) returned to a BCVA of Grade 0 or 1 later during treatment/follow-up, with 87.5% (7) able to start reading again while on study (patients may have experienced Grade ≥2 BCVA events after recovery of the first event).

Figure 5. Worst case post-baseline shift in reading among patients with No Difficulty or A Little Difficulty at baseline (N=83)*



13-month follow-up; cut-off date January 31, 2020. BCVA recovery based on routine study-mandated ophthalmic exam.
*Post-baseline assessments were missing for 8 patients (10%). †Patients may have experienced Grade ≥2 BCVA events after recovery of the first event.

Conclusions

These PRO results from the DREAMM-2 study demonstrate general maintenance or improvement of HRQoL, despite transient reductions in vision-related function. Together with clinical efficacy, these data support the use of belamaf in patients with RRMM.

Overall disease symptoms (pain), functioning, and QoL remained stable during treatment. At Week 7, 46% of patients reported a **meaningful improvement in fatigue**, often a difficult-to-manage symptom for patients with RRMM.[13]

Changes in OSDI vision-related functioning were transient; almost three-quarters of the patients with a decline in OSDI vision-related functioning to or beyond the minimum change threshold used here improved after a median of 24 days.

Over **40% of patients continued everyday activities** such as reading and driving with No Difficulty/A Little Difficulty while on treatment. Some patients had to temporarily stop these activities due to changes in their eyesight, though many reported resuming. We were not able to assess resolution in all patients due to missing PRO data, death, study withdrawal, or being lost to follow-up.

Despite ocular symptoms, even in patients with minimal meaningful within-patient reductions in vision-related function, EORTC-QLQ-C30 data suggest that **overall Global Health Status/ QoL, Physical and Role functioning was maintained or improved** during treatment.

DREAMM-2 included heavily pre-treated RRMM patients with few treatment options. The results reported here need to be weighed for each patient and **close collaboration among hematologist/oncologists and eye care professionals is needed to provide optimal care** in relation to the belamaf benefit:risk profile.

Disclosures

RP has received consultancy fees from Takeda, AbbVie, GlaxoSmithKline (GSK), and Celgene, research funding from Takeda, honoraria from Janssen, Takeda, Celgene, and GSK and travel expenses from Janssen, Takeda, and GSK. **SL** has received research funding from Celgene and Takeda, and personal fees from Celgene, Takeda, Amgen, Bristol-Myers Squibb, GSK, Janssen, Merck, and Novartis. **PMV** has received personal fees from Adaptive Biotechnologies, Bristol-Myers Squibb/Celgene, Janssen, Novartis, Oncopeptides and TeneoBio. **SDE** has received consultancy fees and honoraria from GSK. **IG** is an employee of GSK and reports an ownership interest (including stock options but excluding indirect investments) in GSK interest (including stock options but excluding indirect investments) in GSK. **DK** reports consultancy fees from GSK and Triphase Accelerator U.S. Corporation, and reports an ownership interest (including stock options) in Eyeon Therapeutics, Inc. **DS** reports consultancy fees from GSK, Novaliq, and SilkTech. **AL**, **JM** and **AR** are employees of Modus Outcomes.

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Abbreviations

3L, third line; ADC, antibody-drug conjugate; ADCC, antibody-dependent cell-mediated cytotoxicity; ADCP, antibody-dependent phagocytosis; AE, adverse event; ASCT, autologous stem cell transplant; BCMA, B-cell maturation antigen; BCVA, best-corrected visual acuity; BL, baseline; CBR, clinical benefit rate; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EORTC-QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (C30, core 30; MY20, Myeloma 20); FLC, serum free light chain assay; GHS, global health status; HRQoL, health-related quality of life; ICD, immunogenic cell death; MECs, microcyst-like epithelial changes; MM, multiple myeloma; MMAF, monomethyl auristatin F; MoA, mechanism of action; NEI-VFQ-25, National Eye Institute Visual Function Questionnaire-25 item; OSDI, Ocular Surface Disease Index; PD, progressive disease; PIs, proteasome inhibitors; PRO, patient-reported outcome; Q3W, every 3 weeks; QoL, quality of life; RRMM, relapsed/refractory multiple myeloma; TTP, time to progression; TTR, time to response; VRF, vision-related function.

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