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ORIGINAL RESEARCH

Patient-Reported Outcomes With Belantamab Mafodotin Treatment in Patients With Triple-Class Refractory Multiple Myeloma

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

In the randomized phase II DREAMM-2 study, single-agent belantamab mafodotin demonstrated deep and durable responses and a manageable safety profile in triple-class refractory relapsed/refractory multiple myeloma (RRMM). We present patient-reported outcomes (PROs) from this study for patients treated with the approved dose of belantamab mafodotin (2.5 mg/kg q3w). Disease and treatment-related symptoms, health-related quality of life (HRQOL), functioning, and patient-reported ocular changes were assessed using questionnaires (European Organisation for Research and Treatment of Cancer Quality of Life questionnaires EORTC-QLQ-C30 and EORTC-QLQ-MY20, Ocular Surface Disease Index [OSDI], and the National Eye Institute Visual Functioning Questionnaire 25 [NEI VFQ-25]) at baseline, during treatment (every 3 or 6 weeks), and at the end of treatment (EOT). Eye examinations were conducted at baseline, prior to each treatment cycle, and at EOT. Patients reported ocular symptoms in the OSDI and NEI VFQ-25 questionnaires, with the median time to worst severity of 45 to 64 days depending on symptoms considered. Some limitations in driving and reading were reported. Ocular symptoms were improved and median time to recovery was 23.5 to 44.0 days. EORTC-QLQ-C30 data suggest core MM symptoms (including fatigue and pain), overall HRQOL, and patient functioning were maintained while patients continued belantamab mafodotin treatment, even if meaningful worsening of vision-related symptoms occurred. These PRO results, together with the clinical efficacy of belantamab mafodotin, support its use in patients with RRMM and further evaluation of its use at earlier lines of therapy.

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Multiple myeloma (MM) is a relapsing, incurable hematologic cancer that eventually becomes refractory to treatments. Therapies to treat relapsed/refractory MM (RRMM) aim to control disease progression, prolong survival, reduce disease-related symptoms, and optimize health-related quality of life (HRQOL) in patients (Sonneveld et al., 2013). Despite the survival gains associated with the introduction of immunomodulatory drugs, proteasome inhibitors, and anti-CD38 monoclonal antibodies, clinical outcomes remain poor, particularly for patients who have received several lines of therapy (Kumar et al., 2017). Disease and patient-related factors (e.g., cytogenetic profile, burden of disease, aggressiveness of relapse, age, fitness, comorbidities, stem cell transplant eligibility), treatment history (e.g., number of prior lines of therapy, response/resistance to treatment), and potential impacts on HRQOL need to be considered when selecting appropriate therapy for RRMM (Goldschmidt et al., 2019).

The HRQOL of patients with MM can be affected by demographic and clinical characteristics such as age, performance status, and comorbidities (Robinson et al., 2016). Multiple myeloma can be associated with a high symptom burden and a subsequent decline in functional performance; therefore, the HRQOL of patients with MM, particularly RRMM, is often compromised. Health-related QOL can be worsened by symptoms such as fatigue and bone pain, but also by treatment-related adverse events (AEs; Despiegel et al., 2019; Kamal et al., 2020; Ramsenthaler et al., 2016; Sonneveld et al., 2013).

Validated patient-reported outcome (PRO) measures provide information directly on the patients' perspectives of their disease and the impact of treatment (Sonneveld et al., 2013). Patient-reported outcomes are increasingly used in oncology trials to evaluate patients' experiences with novel therapies (Giesinger et al., 2021; Nipp & Temel, 2018; Sonneveld et al., 2013), including their physical well-being and tolerance of treatment (Nipp & Temel, 2018). The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30) is a widely used pan-oncology PRO instrument to assess disease and treatment-related symptoms, HRQOL, and functioning (ability to perform activities of daily life; Fayers et al., 2002), and the EORTC QLQ-Myeloma 20 (EORTC-QLQ-MY20) is an important MM-specific PRO questionnaire (Cocks et al., 2007). The use of PROs to access direct patient reporting of specific symptomatic organ-system specific AEs is also increasing.

B-cell maturation antigen (BCMA) is expressed on MM plasma cells and is essential for their proliferation and survival (Lee et al., 2016; O'Connor et al., 2004). BCMA-targeting therapies represent an important new approach for treating RRMM (Abramson, 2020). Belantamab mafodotin (belamaf; Blenrep) is a first-in-class antibody-drug conjugate (ADC) comprising a humanized, afucosylated BCMA monoclonal antibody conjugated to the microtubule inhibitor, monomethyl auristatin F (MMAF; Tai et al., 2014).

In the pivotal phase II DREAMM-2 study (205678; NCT03525678), treatment with single-agent belantamab mafodotin 2.5 mg/kg resulted in deep and durable responses and had an acceptable safety profile in patients with triple-class refractory RRMM (Lonial et al., 2020; Lonial et al., 2021). However, as reported with other MMAF-containing ADCs (Eaton et al., 2015), belantamab mafodotin was associated with corneal events (Farooq et al., 2020). In DREAMM-2, the most frequently reported corneal event was keratopathy, including superficial punctate keratopathy and/or microcyst-like epithelial changes (an eye exam pathological finding observed on slit lamp microscopy, with or without symptoms or changes in best-corrected visual acuity [BCVA]). The most common ocular symptoms were blurred vision, dry eye, and decline in BCVA (Lonial et al., 2020; Lonial et al., 2021). Long-term follow-up demonstrated that these changes in vision were generally transient, mild-to-moderate, and led to very few treatment discontinuations (Lonial et al., 2020; Lonial et al., 2021). Given the corneal events reported with belantamab mafodotin, the impact of ocular symptoms on patients' QOL was assessed in DREAMM-2. Although not specifically designed for this purpose, the Ocular Surface Disease Index (OSDI; Schiffman et al., 2000) and the National Eye Institute Visual Functioning Questionnaire 25 (NEI VFQ-25) were employed (Mangione et al., 2001).

The aim of the current analysis was to describe the experience of patients with MM treated with belantamab mafodotin at the approved 2.5 mg/kg dose, in terms of cancer symptoms, tolerability, and functioning in the DREAMM-2 study. A specific component of this objective was to gain a better understanding of the impact of corneal events from the patient perspective that can also aid practitioners and health-care professionals in supporting patients through treatment.

METHODS

Study Design and Patients

DREAMM-2 is an open-label, two-arm, randomized, multicenter, phase II study to evaluate the efficacy and safety of single-agent belantamab mafodotin (2.5 or 3.4 mg/kg IV every 3 weeks, until disease progression or unacceptable toxicity) in patients with RRMM (Lonial et al., 2020). Eligible patients were aged ≥ 18 years, had Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 2, had undergone autologous stem cell transplantation (> 100 days before enrolment) or were considered ineligible for a transplant, and had disease progression on or after receiving ≥ 3 previous lines of antimyeloma therapy (refractory to an immunomodulatory agent, a proteasome inhibitor, and refractory and/or intolerant to an anti-CD38 monoclonal antibody). The primary endpoint of DREAMM-2 was overall response rate. Key secondary endpoints included efficacy (duration of response, time to response, progression-free survival, overall survival, proportion of patients achieving clinical benefit), safety (AEs, serious AEs, and AEs of special interest, including ocular AEs), and other secondary endpoints included PROs and HRQOL (Farooq et al., 2020; Lonial et al., 2020). The study was performed 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. Individual participant data will not be shared. Patients were enrolled between June 2018 and January 2019 (Appendix A; please see the online version for all appendices). Further details can be found in Lonial and colleagues' article (2020). This analysis reports findings for patients receiving belantamab mafodotin at the approved 2.5 mg/kg dose.

Patient-Reported Outcome Assessments

Patients used a tablet to complete PRO questionnaires electronically at baseline and every 6 weeks (EORTC questionnaires) or every 3 weeks during treatment (OSDI and NEI VFQ-25 questionnaires), ahead of clinical discussions at study visits, as well as during the end of treatment (EOT) visit (occurring within 45 days after the last belantamab mafodotin dose). Patients who were not able to complete the self-administered version of the questionnaire on their own and required assistance, used an interviewer-administered format.

Disease-Related Patient-Reported Outcomes

Disease-related symptoms, impact on functioning, and HRQOL were evaluated using the EORTC-QLQ-C30 and the EORTC-QLQ-MY20 (Cocks et al., 2007; Fayers et al., 2002; Popat et al., 2020). The 30-item general cancer-specific EORTC-QLQ-C30 comprises five functional scales (Physical Functioning, Role Functioning, Emotional Functioning, Social Functioning, and Cognitive Functioning), three symptom scales (Fatigue, Nausea/Vomiting, and Pain), six single-item scales (Dyspnea, Appetite Loss, Sleep Disturbance, Constipation, Diarrhea, and Financial Impact) and a Global Health Status/QOL scale (Fayers et al., 2002). The scales and single-item measures are scored from 0 to 100. For the functional scales and Global Health Status scale, higher scores denote a better level of functioning, while a higher score on the symptom scales indicates a greater level of symptoms (EORTC Quality of Life, 2020).

The 20-item EORTC-QLQ-MY20 incorporates assessment of myeloma disease symptoms (reported here), side effects of treatment, body image, and future perspective (Cocks et al., 2007). All scale scores range from 0 to 100, with higher scores indicating worse symptoms for the specific disease symptoms domain (Sully et al., 2019).

Tolerability and Ocular-Related Patient-Reported Outcomes

To address the impact of belantamab mafodotin-induced keratopathy on symptoms and visual function, patients completed the 12-item OSDI, comprising Ocular Symptoms, Vision-Related Functioning, and Environmental Triggers domains

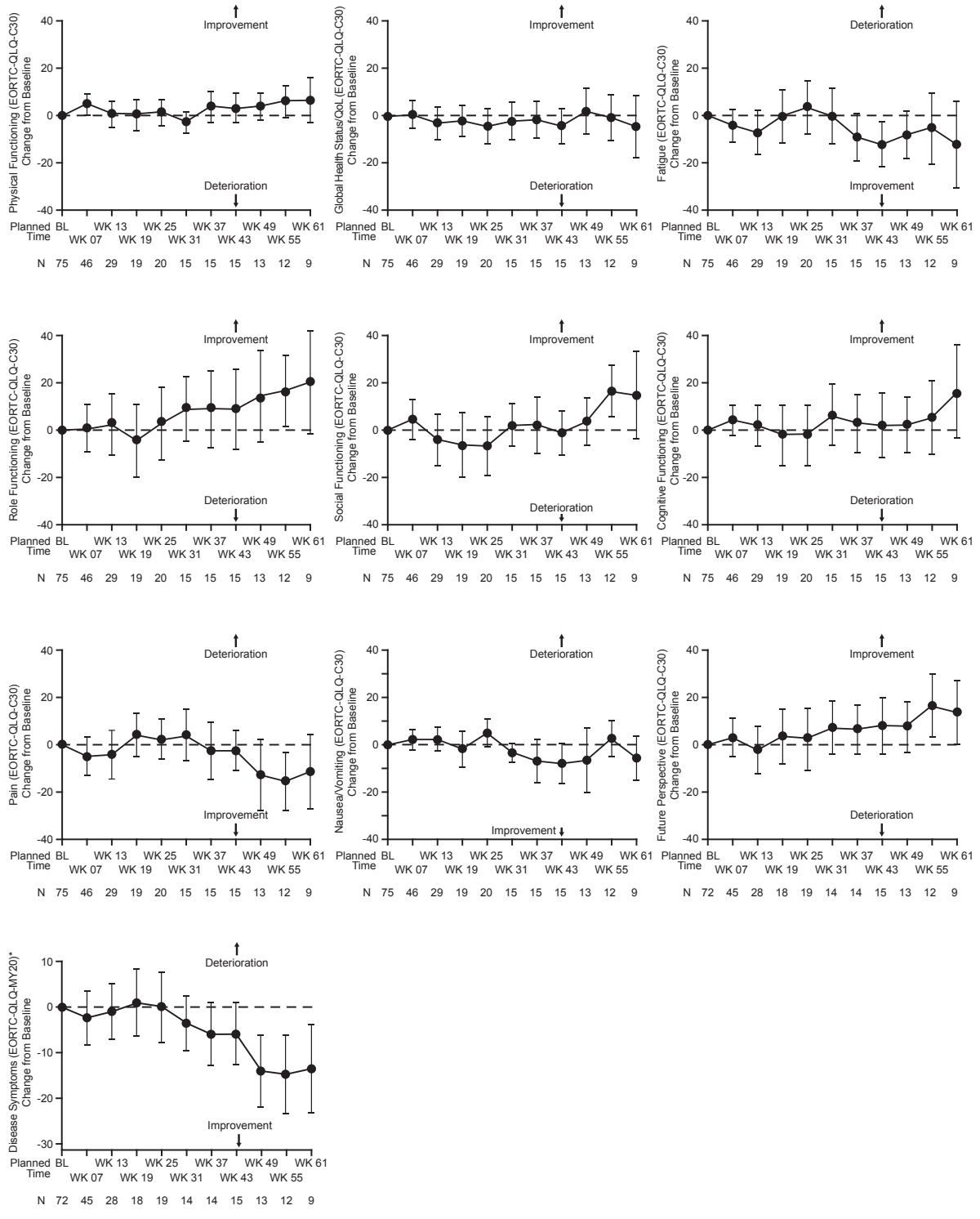


Figure 1. Change from baseline in EORTC-QLQ-C30 and EORTC-QLQ-MY20 in patients remaining on treatment. Median 12.4-month follow-up. Data cut-off date: January 31, 2020. Error bars show 95% CIs. BL = baseline; CI = confidence interval; GHS/QOL = global health status/quality of life; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC-QLQ-MY20 = EORTC-QLQ-Myeloma 20; WK = week.
*Pain in different locations.

related to dry eye (Schiffman et al., 2000). The Vision-Related Functioning domain covers items including blurred vision, poor vision, driving, and reading. The items are graded on a scale of 0 to 4 (0 indicates none of the time; 1, some of the time; 2, half of the time; 3, most of the time and 4, all the time); the overall range of scores is from 0 to 100, with higher scores indicating worse outcomes.

The impact of ocular symptoms on vision and functioning was also assessed using the 25-item NEI-VFQ-25 questionnaire, which measures vision-related QOL and functioning/impact on a scale from 0 to 100, with higher scores denoting better outcomes (Mangione et al., 2001; Popat et al., 2020). Assessment of how visual impairment affected the ability to drive or read (using the NEI VFQ tool) was also included in the current analysis.

The Patient Reported Outcome version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) was also collected to evaluate a range of potential symptomatic AEs (data reported elsewhere; Regnault et al., 2021).

Ocular Examinations

Eye examinations were conducted at baseline, every 3 weeks prior to each treatment cycle, and during the EOT visit by an ophthalmologist or optometrist. They included (at minimum) a slit lamp examination to identify changes in the cornea (keratopathy events) and a BCVA assessment to evaluate changes from baseline (Farooq et al., 2020). Eye examination findings were graded according to the GSK Keratopathy and Visual Acuity (KVA) scale, which was developed for this study by GSK with regulatory agency input (Appendix B; Farooq et al., 2020; GSK, 2020a, 2020b).

All keratopathy events with or without BCVA changes were intended to be followed by an ophthalmologist/optometrist until resolution of changes or recovery to baseline (Farooq et al., 2020). Patients with corneal events at EOT visit were followed up at 3 and 6 weeks and thereafter every 6 weeks for up to 12 months, until resolution of ophthalmic changes, or until deemed clinically stable by the eye care professional, whichever came first.

Recovery of keratopathy was defined as an event that was deemed clinically stable by the eye care professional (grade 1 eye examination finding or no exam finding per KVA scale), and either a 1-line decrease in Snellen BCVA or no change in BCVA compared with baseline (Farooq et al., 2020).

Statistical Analysis

Patient-reported outcomes data from patients who received belantamab mafodotin 2.5 mg/kg (the dose selected for clinical development and approved to treat RRMM; GSK, 2020a, 2020b) were included in the analysis. Results are reported using descriptive statistics (Lonial et al., 2020; Lonial et al., 2021). The data cutoff was January 31, 2020 (after a median follow-up of 12.4 months). A responder analysis of the disease-related PROs was used to evaluate the within-patient change in score from baseline at each assessment timepoint.

A meaningful change in EORTC-QLQ-C30 and EORTC-QLQ-MY20 scores was defined as a within-patient ≥ 10-point shift in either direction from baseline (Osoba et al., 1998; Schjesvold et al., 2020). The current analysis of OSDI data focuses on ocular symptoms and Vision-Related Functioning. For more granular evaluation, specific ocular symptoms were evaluated at the item level. For OSDI, a meaningful change was defined as within-patient shift from baseline of ≥ 12.5 points (at any assessment timepoint and in either direction) based on recommended methods (Grubbs et al., 2014; Schiffman et al., 2000); this threshold was used to quantify treatment-related corneal events in patients with RRMM receiving belantamab mafodotin (Eliason et al., 2020a). Recovery from worst severity post-baseline was also defined as a ≥ 12.5-point improvement in OSDI score (Popat et al., 2020).

An additional analysis assessed change in EORTC-QLQ-C30 Global Health Status/QOL, Physical Functioning, and Role Functioning scores in patients who had a ≥ 12.5-point (Grubbs et al., 2014; Schiffman et al., 2000) deterioration in Vision-Related Functioning on the OSDI.

Ethics Approval and Consent to Participate

The study was done 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.

Table 1. Baseline Demographics and Clinical Characteristics of Patients Receiving Belantamab Mafodotin 2.5 mg/kg in DREAMM-2

	Belantamab mafodotin 2.5 mg/kg (*N* = 97)
Age, years; median (range)	65.0 (60–70)
Female, *n* (%)	46 (47)
ISS stage at screening, *n* (%)	
I	21 (22)
II	33 (34)
III	42 (43)
Unknown	1 (1)
High-risk cytogenetic markers, *n* (%)	
17p13del	16 (16)
t(4;14)	11 (11)
t(14;16)	7 (7)
1q21+	25 (26)
Type of myeloma, %	
IgG	67
Non-IgG or unknown	33
Extramedullary disease, *n* (%)	22 (23)
Prior therapies	
Median (range)	7 (3–21)
≤ 4 lines, n (%)	16 (16)
> 4 lines, n (%)	81 (84)
Refractory to prior therapies, *n* (%)[a]	
Proteasome inhibitor	
Bortezomib	74 (76)
Carfilzomib	63 (65)
Immunomodulatory drug	
Lenalidomide	87 (90)
Pomalidomide	84 (87)
Anti-CD38 monoclonal antibody	
Daratumumab	97 (100)
Isatuximab	3 (3)

Note. Ig = immunoglobulin; ISS = International Staging System. Information from Lonial et al. (2020).
[a]All patients were refractory to a proteasome inhibitor, immunomodulatory drug, and an anti-CD38 monoclonal antibody as per eligibility criteria.

Data Availability Statement

Information about GSK's data-sharing commitments and access requests to anonymized individual participant data and associated documents can be requested for further research at www.clinicalstudydatarequest.com.

RESULTS

Patients

A total of 97 triple-class refractory patients enrolled in DREAMM-2 received belantamab mafodotin 2.5 mg/kg. The median (range) age was 65.0 (60–70) years, and the median number of prior therapies was 7 (3–21); 16/97 (16%) of these patients had received ≤ 4 prior treatments. At screening, 42/97 (43%) of patients had International Staging System Stage III RRMM (Table 1).

Disease-Related Patient-Reported Outcomes

The overall completion rate of the disease-related PRO instruments among patients still in the study at each visit was > 70% for the majority of study visits, indicating moderate adherence (Appendix C).

EORTC-QLQ-C30

A total of 75/97 patients completed the EORTC-QLQ-C30 questionnaire at baseline. Physical Functioning, which measures the ability to do essential tasks (such as walking up the stairs, carrying groceries, etc.), and Global Health Status/QOL domains were maintained over time during belantamab mafodotin treatment (Figure 1). Fatigue (weakness in arms or legs, becoming easily tired, lacking energy) and Role Functioning (limitations to work, daily activities, or leisure activities) domains also showed stability; similar results were seen with Social Functioning (interference with family life or social activities), Future Perspective (thinking about illness, worry about dying/future), and Pain (overall pain and interference) domains (Figure 1).

At Week 7, out of 46 patients remaining on treatment, meaningful (Osoba et al., 1998) improvements from baseline in Physical Functioning domain scores were seen in 13 patients; 30 patients remained stable and 3 reported worsening. At the same timepoint, 21/46 and 14/46 of patients remaining on treatment improved their Fatigue and Pain scores, respectively; 6/46 and 19/46 remained stable, while 19/46 and 13/46 experienced worsening. At Week 25, of 20

Table 2. Changes in OSDI Ocular Symptom Scales and Eye Care Professional Examination Findings

	OSDI Ocular Symptom items					Eye examination findings per KVA scale			CTCAE scale	
	"Eyes sensitive to light" (*n* = 81)	**"Eyes that feel gritty" (*n* = 88)**	**"Painful or sore eyes" (*n* = 89)**	**"Blurred vision" (*n* = 83)**	**"Poor vision" (*n* = 80)**	**Keratopathy (*n* = 95)**	**BCVA (*n* = 95)**	**Keratopathy + BCVA (*n* = 95)**	**Blurred vision (*n* = 95)**	**Dry eye (*n* = 95)**
OSDI worsening from none/some to half of the time or worse, *n* (%)	29 (36)	30 (34)	27 (30)	42 (51)	34 (43)	NA	NA	NA	NA	NA
Eye examination or CTCAE findings, *n* (%)	NA	NA	NA	NA	NA					
Any grade						68 (72)	51 (54)	68 (72)	24 (25)	14 (15)
Grade ≥ 2						60 (63)	44 (46)	61 (64)	13 (14)	5 (5)
Median time to worst-case or time to first occurrence (non-OSDI items), days	64	55	45	51.5	45	37	64	36	51.5	42
Recovered[a] from event by the time of last follow-up, *n* (%)	20 (69)	22 (73)	20 (74)	27 (64)	24 (71)	46 (77)	34 (77)	45 (74)	16 (67)	12 (86)
Missing data (no follow-up PRO), *n* (%)	3 (10)	4 (13)	5 (19)	7 (17)	3 (9)	NR	NR	NR	NR	NR
Median time to recovery[a], days	43.0	34.5	23.5	44.0	42.0	86.5	33.0	96.0	42.5	39.0

Note. BCVA = best corrected visual acuity; CTCAE = Common Terminology Criteria for Adverse Events; KVA = Keratopathy and Visual Acuity; NA = not applicable; NR = not reported; OSDI = Ocular Surface Disease Index; PRO = patient-reported outcome. Median 12.4-month follow-up. Data cut-off date: 31 January 2020. Information from Farooq et al. (2020).
[a]Recovery defined as ≥ 12.5-point improvement.

patients remaining on treatment, 4, 7 and 4 patients still had meaningful improvements in Physical Functioning, Fatigue, and Pain scores, respectively; 14, 6, and 9 patients remained stable and 2, 7, and 7 reported worsening, respectively (Figure 2).

EORTC-QLQ-MY20

A total of 72/97 patients completed the EORTC-QLQ-MY20 questionnaire at baseline. The Disease Symptoms domain showed stability during treatment with belantamab mafodotin (Figure 1 and Appendix D). Improvement in the domain score was observed from Week 31 in the few patients ($n \leq 15$) remaining on treatment and may have been driven by an item focusing on bone pain. At Weeks 7 and 13, meaningful improvements (Schjesvold et al., 2020) in "Disease Symptoms" were observed for 17/45 and 8/28 of patients remaining on treatment; 18/45 and 13/28 patients remained stable, and 10/45 and 7/28 patients reported worsening, respectively. At Week 25, meaningful improvements were observed in 7/19 of patients (Figure 2); 4/19 patients remained stable and 8/19 patients reported worsening. The proportion of patients remaining on treatment and reporting no bone pain at Week 31 was 8/17, compared to 18/72 at baseline; while the proportion of patients reporting "very much" bone pain while on treatment was to 2/17 at Week 31 compared to 11/72 at baseline (Appendix E). At Week 7, of 44 patients with available data who remained on treatment, 8 patients reported worsening of bone pain by 1 or 2 categories (0 patients by 3 categories), 23 were stable (no category change), and 13 reported any level of improvement; by Week 49, of 13 patients remaining on treatment who completed the questionnaire, none reported worsening, 7 reported improvements in bone pain, and 6 remained stable (Appendix F).

Ocular-Related Patient-Reported Outcomes and Eye Examinations

At data cutoff (January 31, 2020) for the OSDI and NEI-VFQ-25 analyses, ocular-related PRO data were available for 92/95 (97%) of patients. Completion of the ocular-related PRO instruments at each study visit was generally high (frequently 80%–90% or above; Appendix C).

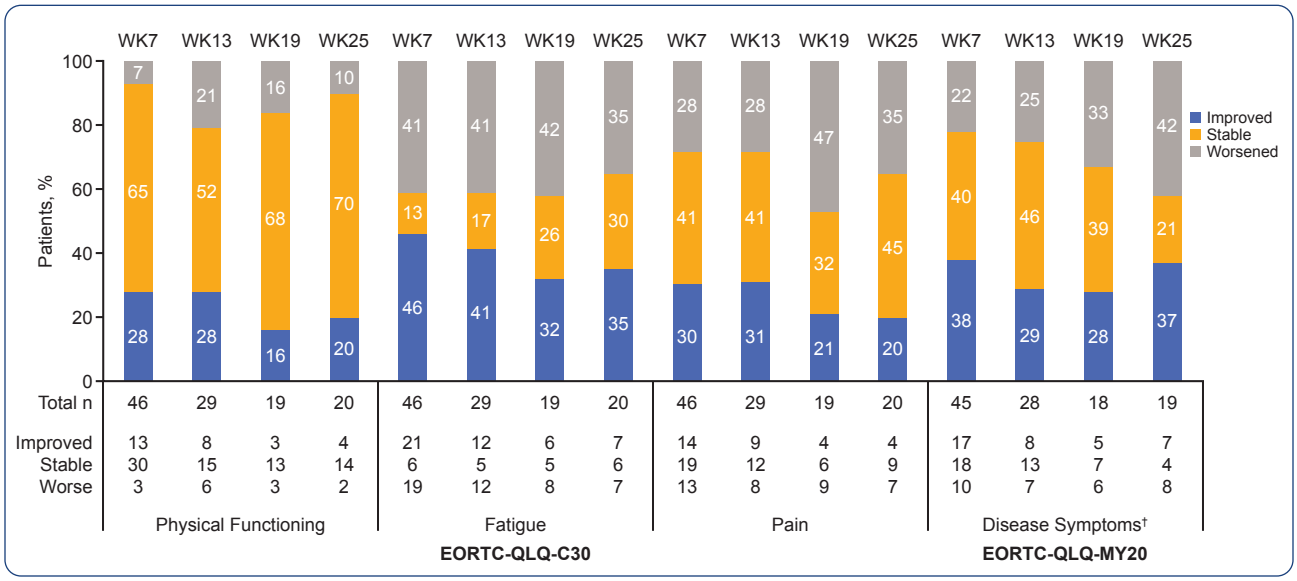


Figure 2. Distribution of patients with meaningful changes from baseline in EORTC-QLQ-C30 and EORTC-QLQ-MY20 domain scores. 13-month follow-up. Data cut-off date: January 31, 2020. Data shown above bars are the number of patients with improvement/number of patients assessed at each study visit. EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC-QLQ-MY20 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Myeloma 20; WK = week.
*Improved: patients with >10-point improvement; Stable: patients with scores between 10-point improvement and 10-point deterioration; Worsened: patients with ≥ 10-point deterioration.
†Pain in different locations.

Ocular Surface Disease Index

Response distributions over time for the five OSDI ocular symptom items are shown in Figure 3. Among patients who reported individual symptoms on the OSDI as "none/some of the time" at baseline, the number who reported worsening of OSDI to "half of the time" or worse throughout the trial was 29/81 for "Eyes sensitive to light," 30/88 for "Eyes that feel gritty," 27/89 for "Painful or sore eyes," 42/83 for "Blurred vision," and 34/80 for "Poor vision." Depending on the ocular symptom considered (e.g., sensitivity to light seemed to be severe later than sore eyes), the median time to the worst severity of the symptom was 45 to 64 days. Most patients (64%–74%) showed recovery of OSDI ocular symptoms by the time of the last available assessment, and median time to recovery, calculated from worst-case post-baseline (WCPB) to threshold improvement, ranged from 23.5 to 44.0 days. The timing of worsening of OSDI symptoms and recovery were generally consistent with reporting for BCVA (Table 2).

Worsening of ≥ 12.5 points (Grubbs et al., 2014; Schiffman et al., 2000) in the OSDI Vision-Related Functioning subscale was reported by 47/95 patients (Appendix G) and was comparable with eye care professional examination findings (Table 2). The median time to onset of first occurrence of OSDI Vision-Related Functioning subscale worsening was 44.0 days. Similar to outcomes seen on eye examination findings (Table 2), meaningful improvement of OSDI changes from WCPB were seen in 34/47 of patients (median time to improvement was 24.0 days; Appendix G).

Subanalysis: EORTC-QLQ-C30 Domain Scores in Patients With Deterioration in OSDI Vision-Related Functioning Metrics

In patients with a meaningful worsening in Vision-Related Functioning, the QLQ-C30 Physical Functioning and Role Functioning scores were maintained over time and showed a similar pattern to the overall population of patients remaining on treatment at the same visit. No difference was observed in the overall self-reported Global Health Status/QOL of these patients compared to the overall sample (Figure 4).

NEI-VFQ-25

At baseline, item-level analyses showed that 70/95 patients reported "no difficulty" or "a little difficulty" with driving during the daytime in familiar places (Figure 5). At WCPB, 37/70 patients stated that they continued to drive with "no difficulty" or "a little difficulty" while on treatment; 6/70 patients had "moderate difficulty" with driving during the daytime, 2/70 patients had "extreme difficulty," and 16/70 patients "stopped driving due to eyesight" at some point; 3/70 patients "stopped driving due to other reasons." Post-baseline assessments were missing for the remaining 6/70 patients.

For the 16 patients who stopped driving due to eyesight at some point, median time to onset of first occurrence was 63.5 days; 7/16 patients returned to driving prior to the EOT visit. Of the patients who did not return to driving, 4/9 patients did not have a follow-up PRO assessment, and 5/9 patients had not returned to driving by the end of follow-up (Figure 5). When BCVA was used as a proxy for recovery, 13/16 patients who stopped driving at some point of the study subsequently returned to a BCVA of grade 0 (no change) or 1 (change of 1 line from baseline) in Snellen Visual Acuity during treatment or follow-up (Appendix B).

Additional item-level analysis of the NEI-VFQ-25 revealed that, at baseline, 83/95 patients rated their ability to read ordinary print in newspapers as "no difficulty" or "a little difficulty" (Figure 5). At WCPB, 35/83 patients stated that they were able to read ordinary print with "no difficulty" or "a little difficulty"; 21/83, 13/83, and 8/83 patients had "moderate difficulty" or "extreme difficulty" reading ordinary print, or "stopped reading due to eyesight," respectively. Post-baseline data were missing for 6/83 patients. Among the 8 patients who had to stop reading due to their eyesight, half stopped within 85 days of treatment initiation; 7 patients were able to resume reading during the study (Figure 5), and all 8 patients returned to a BCVA event of grade 0 or 1 during treatment/follow-up (including those who may have experienced grade 2, defined as a decline from baseline of 2 or 3 lines on Snellen Visual Acuity and not worse than 20/200, or greater BCVA events after recovery of the first event).

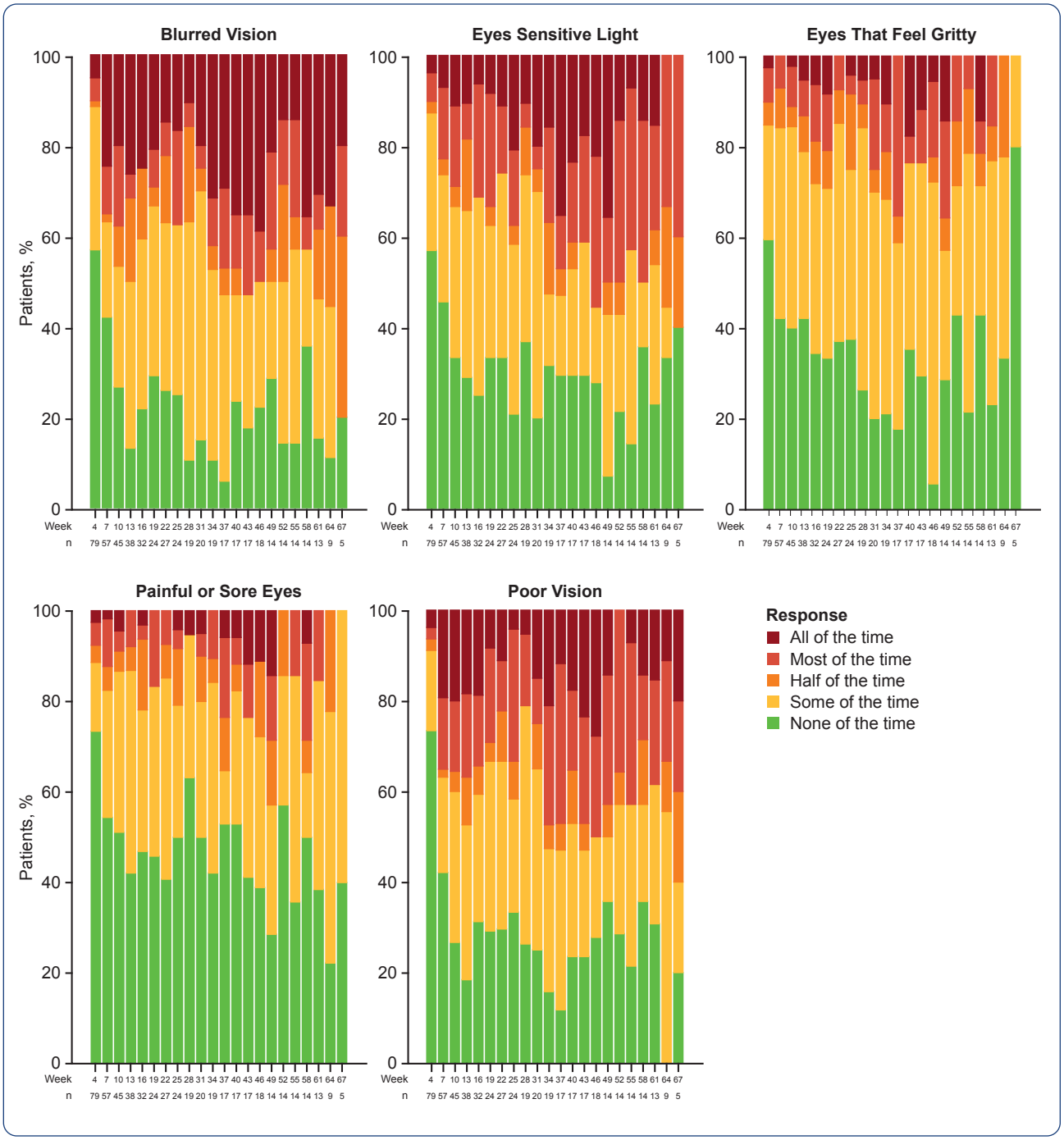


Figure 3. OSDI ocular symptom scale response distributions over time with belantamab mafodotin 2.5 mg/kg. Median 12.4-month follow-up. Data cut-off date: January 31, 2020.
OSDI = Ocular Surface Disease Index.

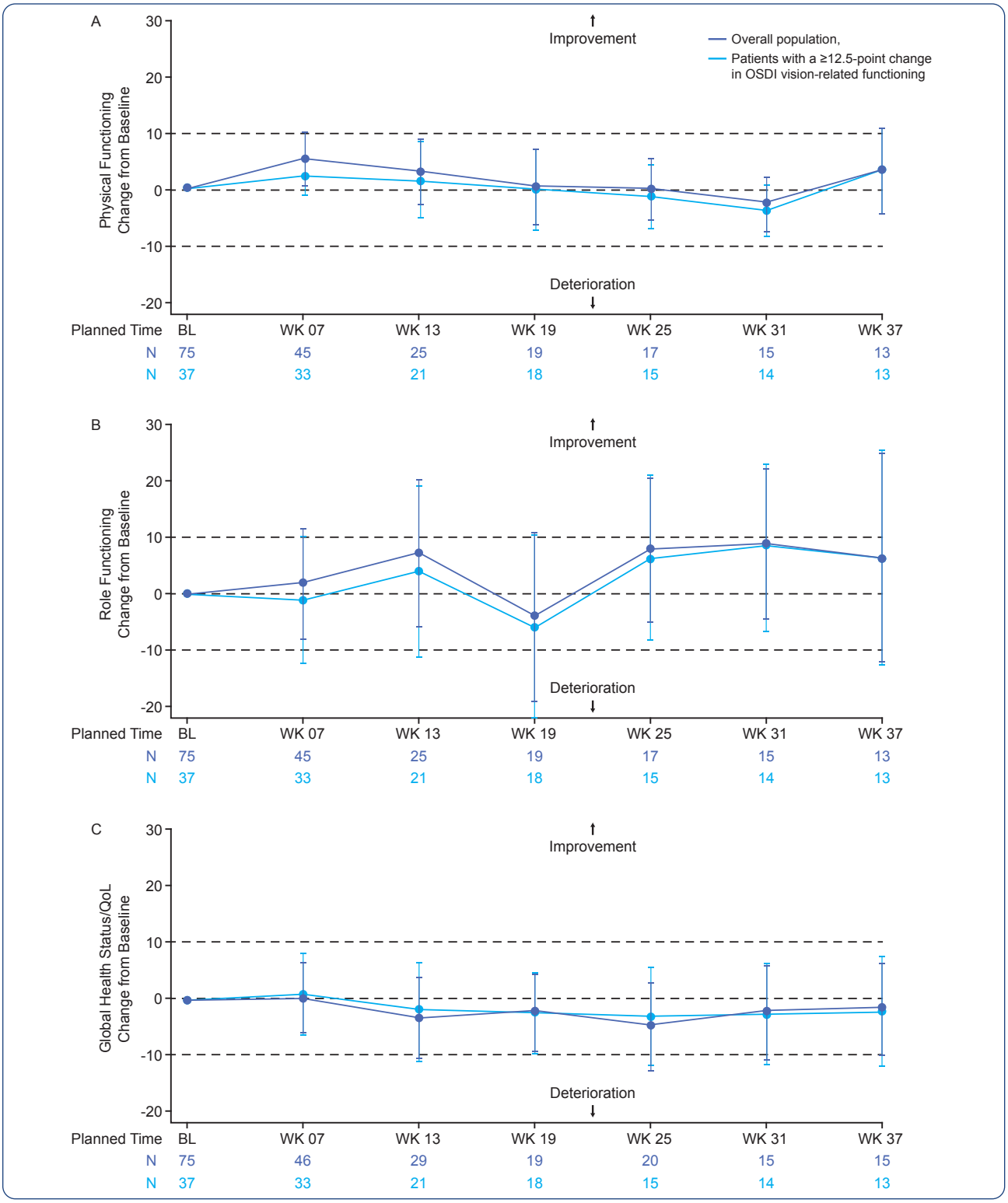
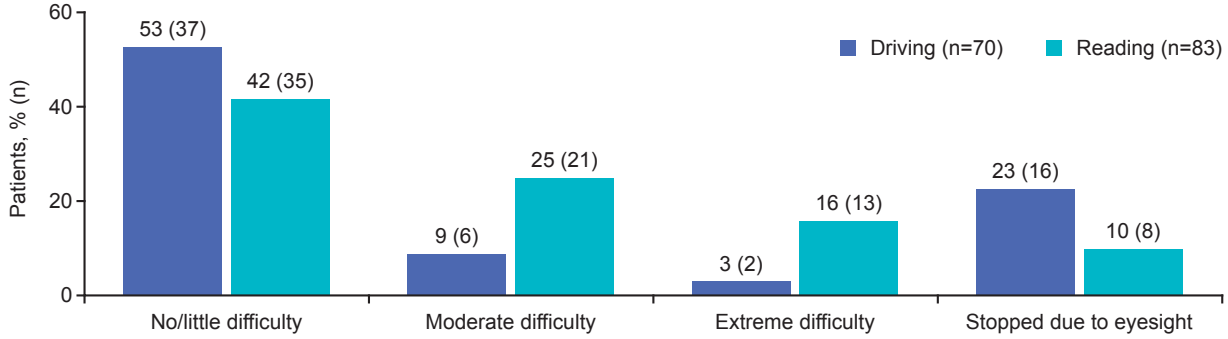


Figure 4. Selected EORTC-QLQ-C30 scores in patients with ≥ 12.5 deterioration in visual function on the OSDI. Median 12.4-month follow-up. Data cut-off date: January 31, 2020. Data are shown for time points with ≥ 10 patients. Error bars show 95% CIs. BL = baseline; CI = confidence interval; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; OSDI = Ocular Surface Disease Index; WK = week.



Outcome in Patients Who Stopped Activity Due to Eyesight, n (%)*	Driving (n=16)	Reading (n=8)
Returned to BCVA Grade 1 or 0 during treatment/in follow-up at any point after stopping	13 (81)	8 (100)
BCVA did not resolve on study	3 (19)	0
Returned to activity	7 (44)	7 (88)
Did not return (follow-up ended)	5 (31)	1 (13)
Did not have a follow-up PRO assessment	4 (25)	0

Figure 5. Worst-case post-baseline change in driving and reading ability among patients with "no/little difficulty" at baseline. Median 12.4-month follow-up. Data cut-off date: January 31, 2020. BCVA = best-corrected visual acuity; PRO = patient-reported outcome.
*In patients who stopped driving or reading due to eyesight, median time to onset of first occurrence was 63.5 and 85 days, respectively.

DISCUSSION

This analysis of the phase II DREAMM-2 study demonstrated that core MM disease symptoms, such as fatigue and pain, as well as patient functioning and overall HRQOL were maintained in patients who remained on treatment with belantamab mafodotin 2.5 mg/kg. Generally, triple-class refractory patients with RRMM have a poor HRQOL (Attal et al., 2019; Delforge et al., 2020; Madduri et al., 2020; Martin et al., 2020; Munshi et al., 2021; Nooka et al., 2020; Richardson et al., 2019) and so it is therefore encouraging that HRQOL was maintained over a median of 12.4 months of follow-up.

Additionally, an improvement in several PRO scores was observed in patients who remained on treatment for a longer period (more than 31 weeks). Overall improvements in the Fatigue score, a symptom often difficult to manage in patients with RRMM, (Dvorak, 2006) and the Disease Symptoms domain, which measures pain in different parts of the body, were observed in patients remaining on treatment. This may, in part, be driven by an item on the EORTC-QLQ-MY20 evaluating bone aches and pains. When evaluating within-patient change, the large majority of patients reported maintained or improved bone pain compared to baseline. Both findings should be further explored in future studies.

Ocular symptoms have been reported following treatment with MMAF-containing ADCs (Eaton et al., 2015; Zhao et al., 2018). In DREAMM-2, at the median 12.4-month follow-up, patient-reported changes in vision and vision-related functioning were of finite duration. Almost three quarters of patients with a decline in OSDI Vision-Related Functioning had meaningful improvement after a median of 24 days. Furthermore, more than 40% of patients continued everyday activities such as reading and driving with "no difficulty/a little difficulty" while on treatment. Although half of the patients experienced reduced ability to continue these activities, most of them recovered by the EOT follow-up.

Resolution was not assessed in all patients due to missing PRO data, death, study withdrawal, or patients being lost to follow-up. However, to date no patients treated with belantamab mafodotin in DREAMM-2 have been recorded as having

confirmed permanent, severe vision changes or loss in either eye (Lonial et al., 2021). Similar to previously published findings, the OSDI symptoms were generally consistent with reporting for BCVA (Farooq et al., 2020).

Despite ocular symptoms, EORTC-QLQ-C30 data suggest that while on treatment, overall Global Health Status/QOL, Physical Functioning, and Role Functioning were maintained during treatment, even in patients with meaningful within-patient reductions in Vision-Related Functioning. Clinician-reported AEs based on the CTCAE (dry eye and blurred vision) were mainly grade 1/2, and changes in BCVA were also manageable with dose modifications and generally resolved by the time of the next eye examination (Lonial et al., 2021). At the median 12.4-month follow-up, 3% of patients had discontinued belantamab mafodotin because of corneal events, suggesting that these events were adequately managed with dose modifications (reduction and/or dose delay) and generally tolerated (Lonial et al., 2021).

The DREAMM-2 trial has shown that belantamab mafodotin is an effective therapy for patients with triple-class refractory RRMM. However, maximizing the benefit of belantamab mafodotin requires optimal understanding and management of AEs. Patient-reported outcomes from the DREAMM-2 trial can help inform the interactions between patients and advanced practitioners (APs), as they help provide the patient perspective of how they experienced the disease-related symptoms of multiple myeloma and ocular-related adverse events of belantamab mafodotin, and the patients' own reflections of their functioning and QOL. Patients need to be informed of the appropriate expectations while on treatment, and this data can serve APs and health-care professionals in the counselling of patients who have been offered belantamab mafodotin. Understanding the PROs can support the discussion between APs and patients by helping APs to answer patients' questions on a practical level (about how they would expect to feel, potential improvements in their myeloma symptoms, potential ocular symptoms, and how much the ocular symptoms may impact their HRQOL). Through this study, the AP will be able to address patients' questions about potential disruption on routine activities, like reading or driving, with insight into the possibility of ocular symptoms occurring while taking belantamab mafodotin. As APs are involved in supporting patients throughout their treatment, the results of this PRO analyses will allow them to advise patients about the reversibility of ocular symptoms seen with belantamab mafodotin and the patient's return to reading and driving, if ocular symptoms have occurred.

Benchmarking against historical and contemporary trials showed that our DREAMM-2 HRQOL data compare favorably. This is particularly noteworthy given that in two chimeric antigen receptor trials used in benchmarking, patients were in a relatively healthy/fit subset of the RRMM population (Appendix H; Attal et al., 2019; Delforge et al., 2020; Madduri et al., 2020; Martin et al., 2020; Munshi et al., 2021; Nolte et al., 2019; Nooka et al., 2020; Richardson et al., 2019) and thus not representative of the general RRMM triple-class refractory population.

Key limitations of our analysis were the open-label nature of the study, which may have influenced reporting, absence of a comparative arm that prevented any causal attribution of effect to belantamab mafodotin, and a modest sample size. Additionally, the changes in EORTC were not assessed specifically during the timing of the event. Although most DREAMM-2 patients in the belantamab mafodotin 2.5 mg/kg group completed the questionnaires at baseline, completion ranged from 66% to 97% for all PRO measures through Week 64 for patients remaining on study. The number of available post-baseline assessments declined over time on study. Approximately one third of the patients included in the study did not have QLQ-C30 or QLQ-MY20 data from Week 19, primarily due to treatment discontinuation. Sample sizes decreased during extended follow-up because patients in DREAMM-2 had advanced disease and may have died or discontinued the study (primarily due to progressive disease; Lonial et al., 2020). Similar declines have been reported for other MM clinical trials (Delforge et al., 2020; Nooka et al., 2020). Additionally, the ophthalmic PROs used in this study were not designed specifically for assessing corneal events associated with pharmaceutical therapy or for use in MM populations; however, they were found to be discriminatory for changes in visual functioning.

Strengths of this analysis include the use of generally validated PRO instruments to evaluate both cancer and AE-related concepts, including the impact of corneal events. Patient trial-embedded interviews were also conducted during DREAMM-2 to evaluate patient experiences of RRMM and belantamab mafodotin treatment; these data are being analyzed separately (Eliason et al., 2020b).

In summary, the DREAMM-2 trial used a comprehensive PRO strategy to not only collect extensive cancer symptoms but also focus on visual functioning due to the known corneal effects of belantamab mafodotin. These data demonstrated that patients with triple-class refractory RRMM who received belantamab mafodotin 2.5 mg/kg generally maintained their HRQOL while on treatment. Vision-related activities were limited during episodes of significant ocular PRO changes; however, these changes were temporary and generally did not adversely impact overall HRQOL and physical functioning. The findings reported here further support the use of belantamab mafodotin for patients with RRMM and highlight the need for a thorough evaluation of its use as an earlier line of therapy. ●

Authorship Contributions

All authors had access to the study data and accept responsibility to submit for publication. All authors were involved at each stage of manuscript preparation and approved the final version. Data were analyzed by Zangdong He and Vinay Jadhav. All authors had access to the primary clinical trial data.

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Disclosure

RP has received consultancy fees from Takeda, AbbVie, 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 Abbvie, Bristol- Myers Squibb/Celgene, Janssen, GSK, Karyopharm, Lava therapeutics, Novartis, Pfizer, Oncopeptides, Regeneron, Sanofi, and SecuraBio. SDE has received consultancy fees from GSK, honoraria from AbbVie, speaker fees from Novartis, Roche, GSK, GenSight Biologics and Bayer UK and travel support from Bayer UK, Roche, GenSight Biologics. BG was an employee of GSK at the time of the study, and holds stocks in GSK and Daiichi-Sankyo. IG was an employee of GSK at the time of the study and reports an ownership interest (including stock options but excluding indirect investments) in GSK and Novartis. JO, SS, TP, and ZH are employees of GSK and report an ownership interest (including stock options but excluding indirect investments) in GSK. DK reports consultancy fees from Emergent Product Development, Ascidian Therapeutics, Inc., Helixmith USA, Kala Pharmaceuticals, ONL Therapeutics, Inc., Opus Genetics, Parsons Medical Communications, Prime Medicine, Blueprint Medicines, AGTC, Editas Medicine, Inc., Aprea Therapeutics, Cleave Biosciences and Synergy Research Inc, holds stocks in ONL Therapeutics, Inc., has leadership or fiduciary role in Eyeon Therapeutics, Inc., Calm Water Therapeutics LLC and Cataract Innovations LLC and has participated in a data safety monitoring board or advisory board for Apellis Pharmaceuticals, Inc. DS reports consultancy fees from GSK, Novaliq, and SilkTech. AR and JM are employees of Modus Outcomes. LE was an employee of GSK at the time of the study.

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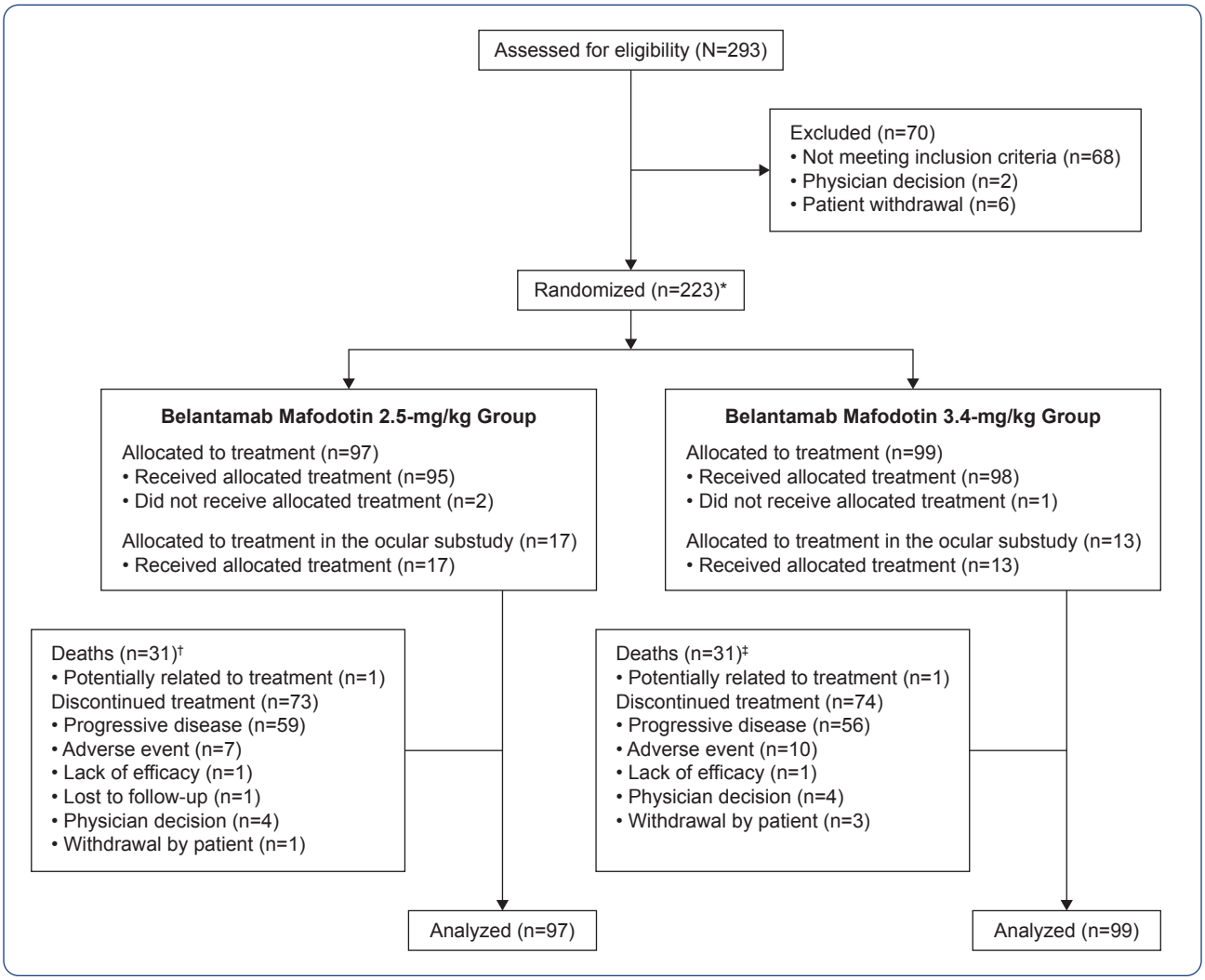


Appendix A. DREAMM-2 (205678; NCT03525678) trial design.

Appendix B. Grading of Corneal Events per GSK Keratopathy and Visual Acuity Scale

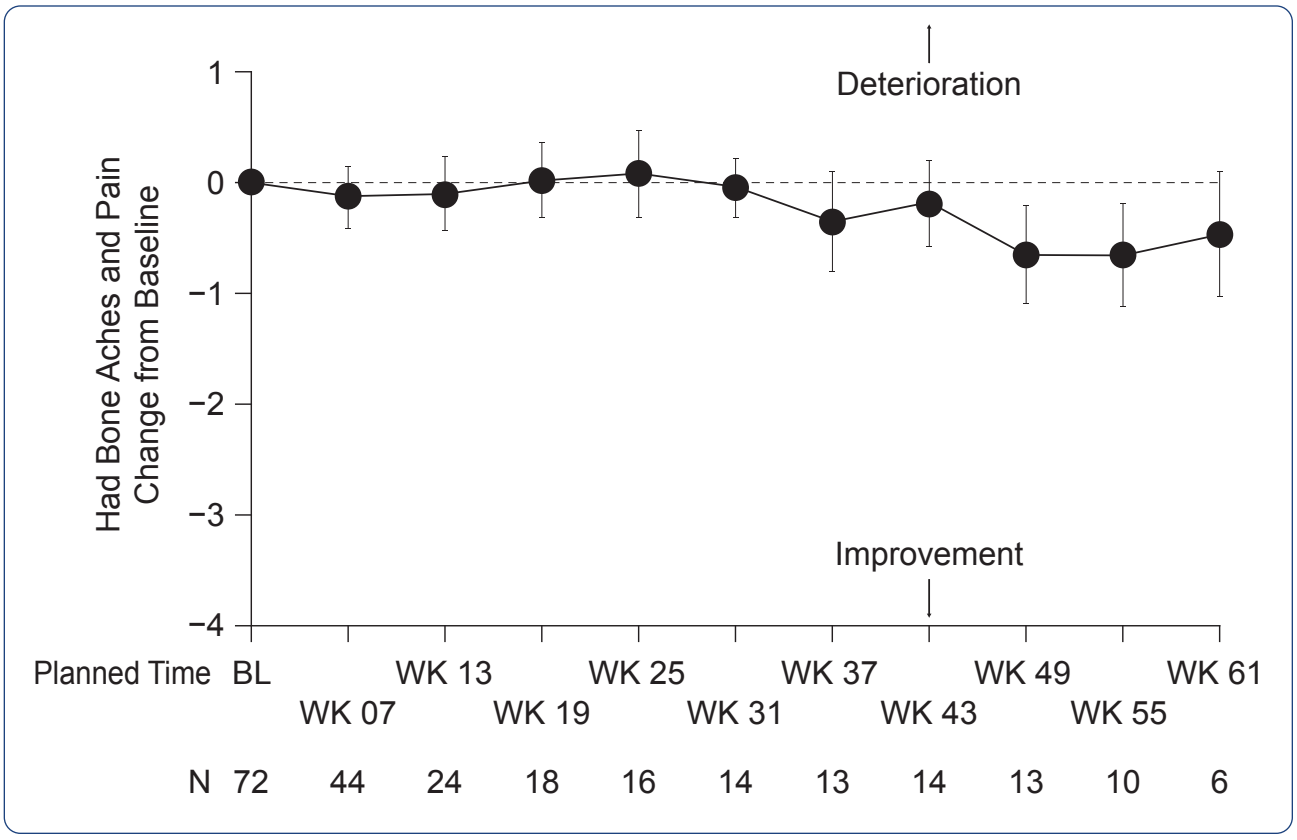
Grade	Corneal examination finding(s)	Change in BCVA[b]
1	Mild superficial keratopathy[a]	Decline from baseline of 1 line on Snellen Visual Acuity
2	Moderate superficial keratopathy[c]	Decline from baseline of 2 or 3 lines on Snellen Visual Acuity and not worse than 20/200
3	Severe superficial keratopathy[d]	Decline from baseline by > 3 lines on Snellen Visual Acuity and not worse than 20/200
4	Corneal epithelial defect[e]	Snellen Visual Acuity worse than 20/200

Note. BCVA = best-corrected visual acuity.
[a]Mild superficial keratopathy (documented worsening from baseline), with or without symptoms.
[b]Changes in visual acuity due to treatment-related corneal findings.
[c]Moderate superficial keratopathy with or without patchy microcyst-like deposits, sub-epithelial haze (peripheral), or a new peripheral stromal opacity.
[d]Severe superficial keratopathy with or without diffuse microcyst-like deposits, sub-epithelial haze (central), or a new central stromal opacity.
[e]Corneal epithelial defect such as corneal ulcers.

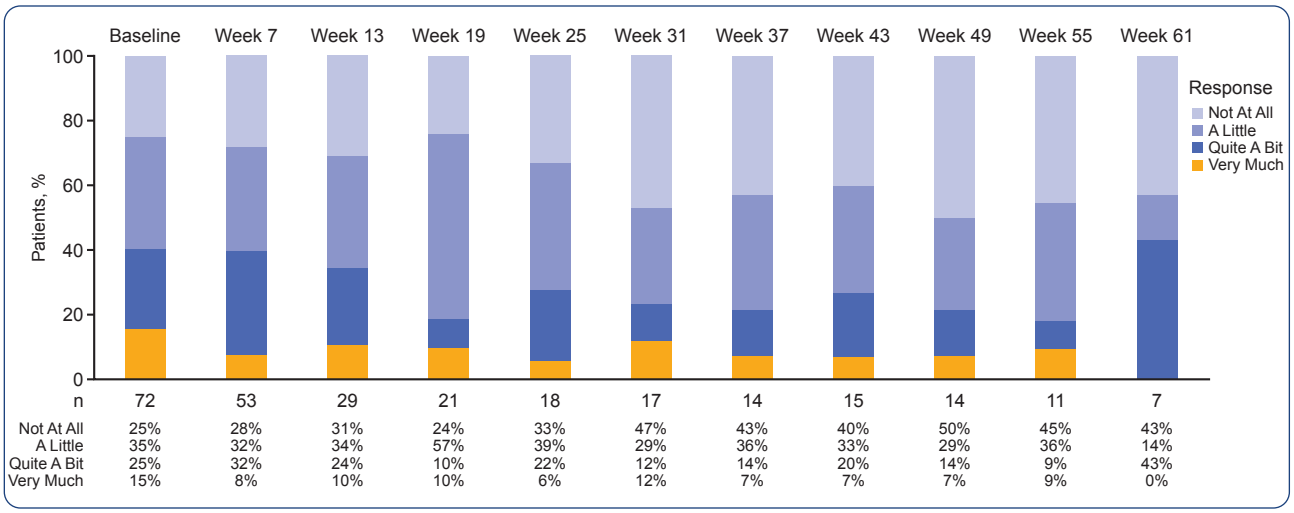
Appendix C. Completion of PRO Instruments in DREAMM-2 by Study Visit for the Belantamab Mafodotin 2.5 mg/kg Group

Compliance by study timepoint, % (*n*/*N*)[a]	Patient-reported outcome instrument			
	EORTC-QLQ-C30	EORTC-QLQ-MY20	NEI-VFQ-25	OSDI
Baseline	77 (75/97)	74 (72/97)	97 (92/95)	97 (92/95)
Week 4	-	-	92 (79/86)	92 (79/86)
7	82 (55/67)	81 (54/67)	85 (57/67)	85 (57/67)
10	-	-	80 (45/56)	80 (45/56)
13	79 (33/42)	79 (33/42)	90 (38/42)	90 (38/42)
16	-	-	91 (32/35)	91 (32/35)
19	66 (21/32)	66 (21/32)	75 (24/32)	75 (24/32)
22	-	-	87 (27/31)	87 (27/31)
25	72 (21/29)	72 (21/29)	79 (23/29)	83 (24/29)
28	-	-	73 (19/26)	73 (19/26)
31	71 (17/24)	71 (17/24)	83 (20/24)	83 (20/24)
34	-	-	86 (19/22)	86 (19/22)
37	76 (16/21)	76 (16/21)	81 (17/21)	81 (17/21)
40	-	-	81 (17/21)	81 (17/21)
43	84 (16/19)	84 (16/19)	89 (17/19)	89 (17/19)
46	-	-	95 (18/19)	95 (18/19)
49	78 (14/18)	78 (14/18)	78 (14/18)	78 (14/18)
52	-	-	82 (14/17)	82 (14/17)
55	81 (13/16)	81 (13/16)	88 (14/16)	88 (14/16)
58	-	-	93 (14/15)	93 (14/15)
61	67 (10/15)	67 (10/15)	87 (13/15)	87 (13/15)
64	-	-	90 (9/10)	90 (9/10)
67	44 (4/9)	44 (4/9)	56 (5/9)	56 (5/9)
70	-	-	25 (2/8)	25 (2/8)
73	17 (1/6)	17 (1/6)	17 (1/6)	17 (1/6)
76	-	-	0 (0/3)	0 (0/3)
79	0 (0/2)	0 (0/2)	0 (0/2)	0 (0/2)
82	-	-	0 (0/1)	0 (0/1)
End of treatment	45 (38/85)	45 (38/85)	56 (48/85)	56 (48/85)
Last follow-up	-	-	7 (5/70)	7 (5/70)

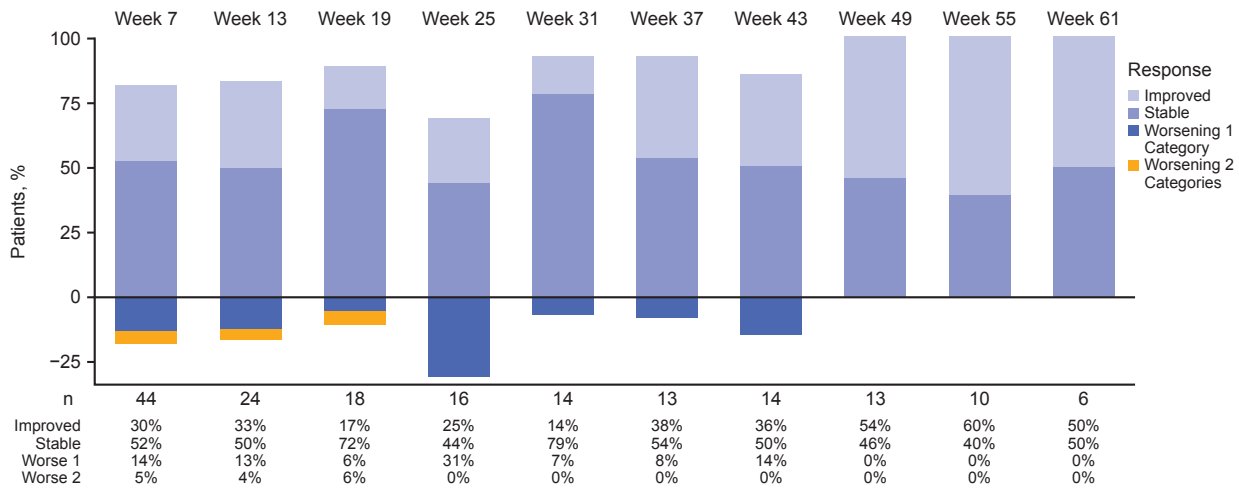
Note. EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC-QLQ-MY20 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Myeloma 20; NEI-VFQ-25 = National Eye Institute Visual Functioning Questionnaire 25; OSDI = Ocular Surface Disease Index; PRO = patient-reported outcome.
[a]Percentage was calculated using number of patients remaining in the study at each timepoint as the denominator.



Appendix D. Change from baseline in EORTC-QLQ-MY20 item "Have you had bone aches or pain?" scores. The item was graded on a scale of 1 to 4, where 1 indicates "Not at all"; 2 = "A little"; 3 = "Quite a bit"; and 4 = "Very much." BL = baseline; EORTC-QLQ-MY20 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Myeloma 20; WK = week.



Appendix E. Response category for EORTC-QLQ-MY20 item "Have you had bone aches or pain?" EORTC-QLQ-MY20 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Myeloma 20.



Appendix F. Change in response category for EORTC-QLQ-MY20 item "Have you had bone aches or pain?" No patients worsened by 3 categories. EORTC-QLQ-MY20 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Myeloma 20.

Appendix G. Meaningful (≥ 12.5-Point) Within Patient Change From Baseline in OSDI Vision-Related Functioning Subscale Scores

	≥ 12.5-point worsening from baseline (*n* = 95)
Patients with event, *n* (%)	47 (49.5)
Time to onset of first occurrence, days median (range)	44.0 (21–231)
Duration of first event, days median (range)	24.0 (7–350)
First event outcomes, n/N (%)	
Recovered[a]	34/47 (72)[b]
Not recovered	13/47 (28)[c]

Note. Median 12.4-month follow-up. Data cut-off date: January 31, 2020. Recovery of keratopathy was defined as an event that was deemed clinically stable by the eye care professional. Clinical stability was defined as any Grade 1 examination finding (per KVA scale) or no exam finding, and either a one-line decline in BCVA or no change in BCVA when compared with baseline.
BCVA = best corrected visual acuity; KVA, keratopathy and visual acuity; OSDI = Ocular Surface Disease Index.
[a]It was not possible to assess recovery in all cases as some patients remained on treatment/in follow-up at the data cut-off date, and some were lost to follow-up, as shown.
[b]Recovery defined as ≥ 12.5-point improvement.
[c]*n* = 3 not improved, *n* = 10 missing.

Appendix H. Baseline QOL Scores for DREAMM-2 (2.5-mg/kg Group) and Other Recent RRMM Trials

	DREAMM-2 belantamab mafodotin 2.5 mg/kg	**KarMMa** idecabtagene vicleucel	**CARTITUDE-1** ciltacabtagene autoleucel	**OPTIMISMM** pomalidomide, bortezomib, and low-dose dexamethasone	**General population normative data**
Patients in PRO analysis (*n*)	75	122	68	240	15,386
Baseline EORTC-QLQ-C30 scores, mean[a]					
GHS/QOL	54.2	60.7	62.2	61.0	66.1
Pain	35.8	39.9	37.0	28.3	23.5
Fatigue	43.4	39.3	37.4	33.2	29.5
Nausea and vomiting	7.6	NR	NR	5.6	5.9
Physical functioning	67.4	69.4	78.6	73.9	85.1
Role functioning	62.0	NR	NR	74.4	84.3
Cognitive functioning	76.4	NR	NR	84.0	84.8
Social functioning	72 (21/29)	NR	NR	79.4	86.2

Note. EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; GHS/QOL = Global Health Status/Quality of Life; NR = not reported; PRO = patient-reported outcome; RRMM = relapsed/refractory multiple myeloma. Information from Lonial et al. (2020); Delforge et al. (2020); Martin et al., 2020; Nolte et al. (2019); Weisel et al., (2020).
[a]Higher mean score indicating worse/higher severity symptoms.