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Real-world effectiveness and safety of belantamab mafodotin monotherapy in patients with relapsed/refractory multiple myeloma treated in Europe

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Author Contributions

MC, **MDe**, **MDi**, **FE**, **DK**, **HCL, RV**, **LC-O**, **JBi**, **TdE**, **MF**, **JBy**, **CYV**, **JM**, and **MH** were involved in study concept or design, data acquisition, data analysis, and data interpretation. **RG**, **TM**, **EA**, **FS**, and **AL** were involved in data acquisition, data analysis, and data interpretation. **SS** and **VSB** were involved in data

interpretation. All authors reviewed and revised the manuscript, approved the final version, and agreed to submit the manuscript for publication.

Data Sharing

Information about GSK's data sharing commitments and access requests to anonymized individual participant data and associated documents can be requested for further research from https://www.gsk-studyregister.com/en/.

Keywords: Belantamab mafodotin; real-world; Europe; multiple myeloma

Belantamab mafodotin is a BCMA-targeting antibody drug conjugate (ADC) consisting of a humanized, afucosylated, IgG antibody conjugated to the microtubule inhibitor monomethyl auristatin F (MMAF) that exerts multiple mechanisms of action.[1] From August 2020 to February 2023 in the United States (US) and August 2020 to February 2024 in Europe, belantamab mafodotin was available as monotherapy for patients with relapsed/refractory multiple myeloma (RRMM) who had received at least 4 prior lines of therapy (LOTs) including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.[2,3] Conditional approval was based on the phase II DREAMM-2 trial.[4] In the phase III DREAMM-3 trial, belantamab mafodotin did not meet the primary endpoint of progression-free survival (PFS) resulting in its withdrawal from European and US markets.[2,3,5]

Belantamab mafodotin has demonstrated robust clinical efficacy in combination regimens for second-line or later RRMM in the DREAMM-7 and DREAMM-8 phase III trials , and the combinations have been approved in multiple countries for patients with RRMM, including Europe.[6]

To mitigate and manage ocular adverse events (oAEs), which have been reported with ADCs containing an MMAF payload including belantamab mafodotin,[7] the European label recommended ophthalmic examinations before the first 4 belantamab mafodotin doses and as clinically indicated thereafter.[8]

Real-world data on belantamab mafodotin monotherapy provide valuable insight to inform clinical decisions, particularly management of oAEs, with recently approved combination regimens. Study objectives were to describe the real-world use, safety, and effectiveness of belantamab mafodotin monotherapy in patients treated across multiple European countries.

This was a multinational, multicenter, non-interventional, prospective study of adults with RRMM who received belantamab mafodotin in routine clinical care in Europe. **Supplementary Figure 1A** depicts the study design, eligibility criteria, and endpoints. All sites obtained Independent Ethics Committee approval. The study duration was planned to be a maximum of 2 years and 3 months per site; however, the study was closed early based on the European Medicines Agency's decision not to renew the license for belantamab mafodotin monotherapy.[2,5]

At data cutoff (June 7, 2024), 84 patients were enrolled across 7 countries and all received ≥1 dose of belantamab mafodotin (**Supplementary Figure 1B**). Median follow-up (impacted by the early study termination) was 7.8 months (interquartile range [IQR] 4.6–13.1).

The median age at diagnosis was 63.5 years (IQR 58.0–71.5). At belantamab mafodotin initiation, median age was 72.0 years (IQR 64.5–78.0), 46 (54.8%) patients were female, and most patients had an Eastern Cooperative Oncology Group performance (ECOG) status of 0 (n=24 [28.6%]) or 1 (n=20 [23.8%]) (data missing for 25 [29.8%]; **Table 1**).

History of eye disease (including dry eye/eye injuries affecting best-corrected visual acuity [BCVA]) was present in 27 (32.1%) patients at baseline (**Supplementary Table 1**), with the eye diseases known for 26 (31.0%) patients.

The median number of prior LOTs was 4 (range 2–11). All patients received a prior immunomodulatory agent (60.7% were refractory to lenalidomide; 69.0% to pomalidomide) and a prior proteasome inhibitor (42.9% were refractory to bortezomib; 52.4% to carfilzomib), and 82 (97.6%) had prior anti-CD38 exposure (78.6% were refractory to daratumumab) (**Table 1**). Concomitant MM treatments were received by 32 (38.1%) patients and concomitant eye medications were received by 69 (82.1%) patients.

Most patients received an initial belantamab mafodotin dose of 2.5 mg/kg (77 [91.7%]) and most were planned to be treated at a Q3W schedule (73 [88.1%]). The median duration of treatment (time-to-event analysis) and median duration of active exposure (period that belantamab mafodotin was considered to have treatment effect) were both 4.1 months (IQR 2.3–7.6).

At baseline, prior to belantamab mafodotin initiation, 65 (77.4%) patients had an ophthalmic examination. Of patients who received a second, third, and fourth dose, 57/76 (75.0%), 41/59 (69.5%), and 31/40 (77.5%), had an ophthalmic examination between administration of the prior dose and administration of the second, third, or fourth dose, respectively. Ophthalmic examination rates remained high for patients with ongoing eye disease at belantamab mafodotin initiation and in patients who had an oAE at any time during the follow-up period (**Figure 1A**).

oAEs occurred in 58 (69.0%) patients (all treatment related), 19 (22.6%) of which were grade ≥3 (**Table 2**); oAEs generally occurred after the first or second dose . The most common oAE was keratopathy (42 [50.0%]), which was mostly mild or moderate at maximum severity per the NCI-CTCAE scale (**Table 2**).

Rates of keratopathy on treatment were relatively higher among patients with an ongoing ophthalmic disease at initiation (14/23 [60.9%]; **Supplementary Table 2**) versus patients without history of

ophthalmic disease (26/57 [45.6%]). Overall, first oAEs resolved or were resolving by the last known visit in 29/58 (50.0%) patients. Considering keratopathy alone, first incidence of keratopathy resolved in 22/42 (52.4%) patients.

Impacts of oAEs on daily living were followed until oAE resolution or until last study visit. Among 42 patients with keratopathy, the most common impact on daily living was eye irritation/pain, which occurred in 13 (31.0%) patients; 10 (23.8%) patients reported reading impairment, 2 (4.8%) reported driving impairment, 1 (2.4%) reported a need for caregiver support, 8 (19.0%) reported other impacts, and 15 (35.7%) patients reported no significant impact (**Figure 1B**).

oAEs led to treatment delay in 37 (44.0%) patients, dose reduction in 13 (15.5%), and treatment discontinuation in 7 (8.3%) (**Table 2**). Among patients with keratopathy who had a dose delay (n=29), the median (IQR) duration of delay was 22.3 days (17.5–35.0).

Among 62 patients evaluable for response, the overall response rate was 38.7% (n=24; 1 patient [1.6%] complete response, 10 [16.1%] very good partial response, 13 [21.0%] partial response). The median duration of response was 10.7 months (95% CI 3.94–not reached). Median real-world PFS (rwPFS) was 4.5 months (95% CI 3.5–5.2) in the overall study population and median OS was not estimable (95% CI 11.0 months–not estimable). These findings have important implications for the integration of belantamab mafodotin into combination regimens, especially in light of the robust efficacy demonstrated recent phase III trials.[9-11]

Patients in this study were slightly older than patients in the DREAMM-2 and DREAMM-3 trials of belantamab mafodotin 2.5 mg/kg Q3W monotherapy and in the real-world study of belantamab mafodotin use in the US,[4,5,12] but similar to the median age reported in real-world studies of patients with MM in Europe.[13]

All patients who had refractory status available were at least triple-class refractory. All patients received an immunomodulator and a proteasome inhibitor in a prior LOT, and nearly all had prior anti-CD38 exposure. Although patients refractory to these agents can achieve treatment responses with later LOTs or with retreatment, the responses are typically shorter compared to the initial treatment.[14,15] Belantamab mafodotin has been evaluated in the second-line-or-later setting as part of combinations in the phase III DREAMM-7 and DREAMM-8 studies, and demonstrated significant survival benefits.[9-11]

At odds with the European label which recommended ophthalmic monitoring before the first 4 doses and as clinically indicated to manage oAEs,[8] the US label required ophthalmic monitoring before each dose, with a Risk Evaluation and Mitigation Strategy program in place to ensure the exams were conducted.[16] Despite these differences, patients in Europe still had a high rate of ophthalmic monitoring prior to each of the first 4 belantamab mafodotin doses (≥69.5%), especially among patients with an ongoing ophthalmic disease at treatment initiation or an oAE at any time during belantamab mafodotin treatment (≥80.0%). Patients with ongoing ophthalmic disease at belantamab mafodotin initiation had higher rates of keratopathy than patients without history of ophthalmic disease, supporting the need for close and active ophthalmic monitoring in patients with ophthalmic disease at treatment initiation. While oAEs are an important consideration when treating with ADCs including belantamab mafodotin, these events can be adequately managed with proper monitoring and dose modification, and the less stringent monitoring recommendations in Europe compared to the US seems to not impact tolerability overall or increase ocular risk.[12] Additionally, the rate of oAEs (69.0%) was similar to that of the DREAMM-2 (74.0%) and DREAMM-3 (66.0%) monotherapy studies despite the use of various concomitant MM therapies in the current study.[4,5]

Reading and driving impairment are particularly important symptoms of oAEs when considering impact on daily living. Though evaluation was limited by small patient numbers and missing data, patients with keratopathy tended to have moderate rates of reading impairment and low rates of driving impairment. A study of patient-reported experiences on belantamab mafodotin indicated that these symptoms resolve over time.[17]

The real-world nature of this study introduces several limitations. As assessment and monitoring criteria are not as stringent as required in clinical trials, bias in reporting, delays in monitoring, or under-identification of oAEs and disease progression may have occurred. The use of electronic health records for collection of retrospective data also has inherent limitations, including the potential for missing or misclassified information. Despite the possibility that assessments of effectiveness were limited by missing data, the rwPFS in this study (median 4.5 months) was consistent with that reported in other real-world studies of belantamab mafodotin monotherapy in heavily pretreated patients.[12] In addition, non-ocular AEs were not assessed, and the NCI-CTCAE grading criteria for AEs were designed for use in clinical trials and not real-world studies. Lastly, the early closure of the study limited the number of patients enrolled and follow-up time, restricting the robustness of efficacy outcomes. A strength of the

study was the use of prospective data; specific guidance for use of belantamab mafodotin beyond that included in the label was also not provided to participating sites, which allowed the study to assess real-world treatment decisions.

Results of this study were generally consistent with those observed in belantamab mafodotin monotherapy clinical trials for RRMM,[4,5] and support the use of label-recommended monitoring strategies as a way for appropriate management and resolution of oAEs with belantamab mafodotin in clinical practice. This experience may guide optimization of monitoring and safety with the combination regimens.[8-11]

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Tables and figures

Table 1. Demographic and disease characteristics

Characteristic	Overall study population (N=84)
Age at belantamab mafodotin initiation, years	
Median (IQR)	72.0 (64.5–78.0)
Age category at belantamab mafodotin initiation, n (%)	
18 to <65 years	21 (25.0)
65 to <75 years	30 (35.7)
75 to <80 years	20 (23.8)
≥80 years	13 (15.5)
Age at initial MM diagnosis, years	
Median (IQR)	63.5 (58.0–71.5)
Female, n (%)	46 (54.8)
ECOG performance status at belantamab mafodotin initiation, n (%)	
0	24 (28.6)
1	20 (23.8)
2	14 (16.7)
3	1 (1.2)
4	0
Missing	25 (29.8)
Time since initial MM diagnosis, months	
Median (IQR)	79.0 (53.2–119.3)
Extramedullary disease* between initial MM diagnosis and belantamab mafodotin initiation, n (%)	
Yes	14 (16.7)
No	66 (78.6)
Unknown	4 (4.8)

ISS stage at initial MM diagnosis, n (%)	
I	21 (25.0)
II	14 (16.7)
III	24 (28.6)
Missing	25 (29.8)
MM subtype at initial MM diagnosis, n (%)	
IgA	13 (15.5)
IgD	1 (1.2)
IgG	43 (51.2)
IgM	0
Biclonal (IgG, IgA)	0
Light chain	18 (21.4)
Other[†]	9 (10.7)
Cytogenetic risk between initial MM diagnosis and belantamab mafodotin initiation, n (%)[‡]	
High cytogenetic risk[§]	23 (27.4)
High risk per IMWG criteria[‖]	17 (20.2)
Standard risk	61 (72.6)
≥1 prior treatment, n (%)	
Immunomodulator	84 (100.0)
Refractory to pomalidomide	58 (69.0)
Refractory to lenalidomide	51 (60.7)
Anti-CD38 exposure	82 (97.6)
Refractory to daratumumab	66 (78.6)
Proteasome inhibitor	84 (100.0)
Refractory to bortezomib	36 (42.9)
Refractory to carfilzomib	44 (52.4)
Chemotherapy	66 (78.6)
Stem cell transplant	41 (48.8)
Bispecific antibody[¶]	1 (1.2)
CAR-T cell therapy[#]	2 (2.4)
Histone deacetylase treatment	1 (1.2)

Number of prior LOTs, n (%)	
2**	7 (8.3)
3**	8 (9.5)
4	36 (42.9)
5	15 (17.9)
6	7 (8.3)
>6	11 (13.1)
Refractory status, n (%)[††]	N=78
Triple refractory or greater	78 (100.0)
Triple refractory	29 (37.2)
Quad refractory	28 (35.9)
Penta refractory	21 (26.9)

*Extramedullary disease was not further classified as soft tissue masses not contiguous with the bone or extraskeletal disease.

[†]Other was reported as “IgG kappa” (n=2) and n=1 each for “IgG lambda,” “Bence-Jones," “plasma cell leukemia (micromolecular),” “micromolecular k,” “plasmocytoma type kappa, since 2015, multiple light chain myeloma kappa,” “non-secretory no phenotype,” and “typ lambda.”

[‡]A patient could be included in both high cytogenetic risk and high risk per IMWG categories. The manner of cytogenetic risk determination was not collected.

[§]High-risk cytogenetics: t(4;14), t(14;16), del17p, or 1q+.

[⁋]High risk cytogenetics per IMWG: t(4;14), t(14;16), or del17p.

[¶]Non-BCMA targeting.

[#]Idecabtagene vicleucel.

**Twelve patients who received <4 prior LOTs were included despite being major protocol violations; 3 patients in Spain who received <4 prior LOTs were included but not considered protocol violations per belantamab mafodotin labeling in Spain, in which belantamab mafodotin was indicated for patients with ≥4 prior therapies and therefore could include patients who received ≥4 individual agents regardless of therapy line.[18]

[††]Refractory status was missing for 6 patients; percents are calculated based on patients with refractory status available. Triple, quad, and penta refractory refer to patients who were refractory to 3, 4, or 5 therapy classes, respectively.

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; ECOG, Eastern Cooperative Oncology Group; IMWG, International Myeloma Working Group; IQR, interquartile range; ISS, International Staging System; LOT, line of therapy; MM, multiple myeloma.

Table 2. Ocular adverse events*

	Overall study population (N=84)
Patients with any oAE, n (%)	58 (69.0)
Treatment-related	58 (69.0)
NCI-CTCAE grade ≥3	19 (22.6)
KVA grade ≥3	19 (22.6)
Leading to dose reduction	13 (15.5)
Leading to treatment interruption/delay	37 (44.0)
Leading to treatment discontinuation	7 (8.3)
Leading to study withdrawal	0
Leading to death	0
Keratopathy, n (%)	42 (50.0)
Mild	11 (13.1)
Moderate	22 (26.2)
Severe	9 (10.7)
Other, n (%)	16 (19.0)
Mild	8 (9.5)
Moderate	6 (7.1)
Severe	1 (1.2)
Missing	1 (1.2)
Corneal erosions or defects, n (%)	7 (8.3)
Mild	2 (2.4)
Moderate	4 (4.8)
Severe	1 (1.2)
Blurred vision events, n (%)	6 (7.1)
Mild	3 (3.6)
Moderate	1 (1.2)
Severe	1 (1.2)
Missing	1 (1.2)
Change in BCVA, n (%)	4 (4.8)
Mild	0

Moderate	2 (2.4)
Severe	2 (2.4)
Dry eye events, n (%)	1 (1.2)
Mild	0
Moderate	1 (1.2)
Severe	0
Photophobia, n (%)	1 (1.2)
Mild	1 (1.2)
Moderate	0
Severe	0

*All percentages calculated using N=84 as the denominator.

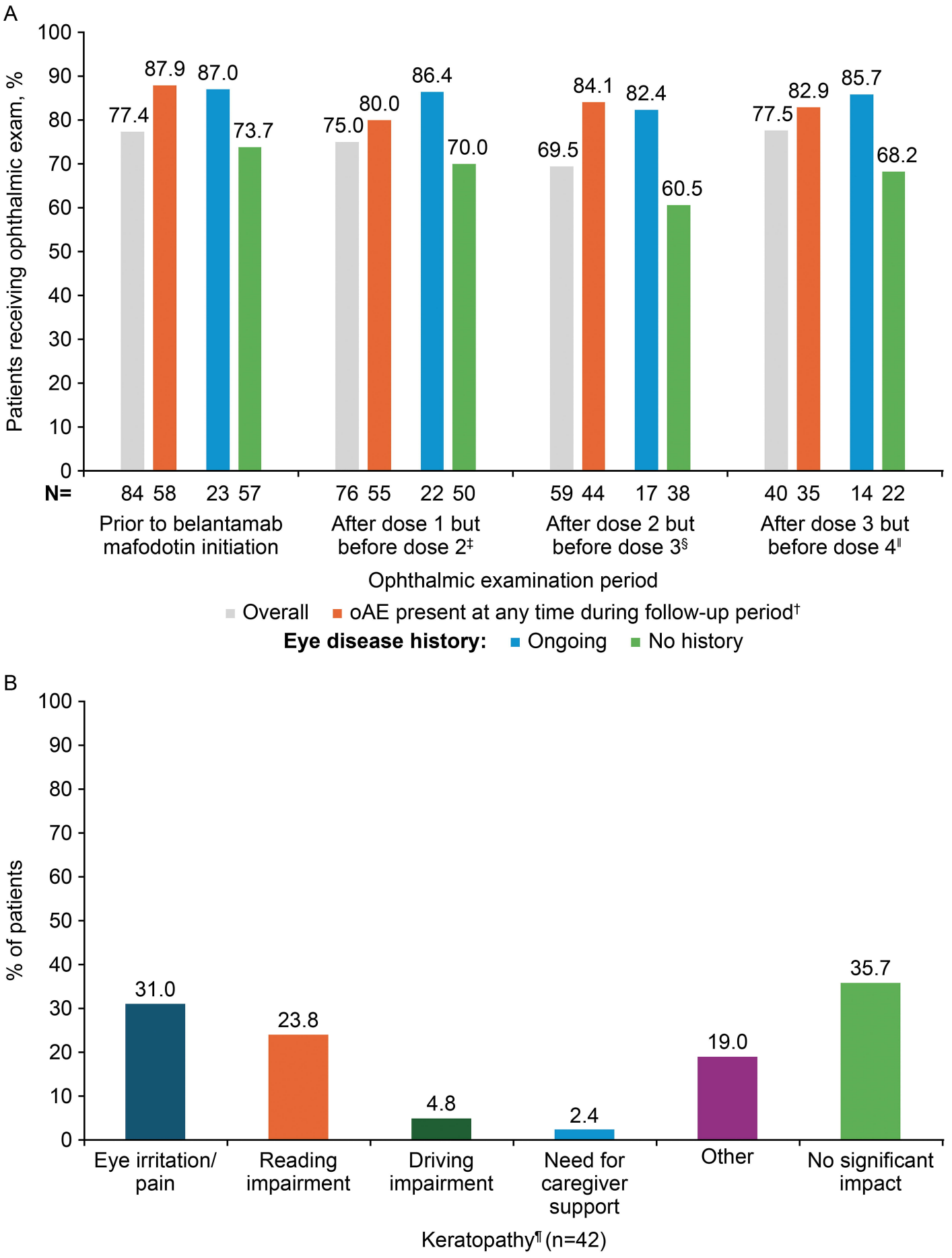
BCVA, best-corrected visual acuity; KVA, Keratopathy and Visual Acuity; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; oAE, ocular adverse event.

Figure 1. Real world ophthalmic examinations in patients with relapsed/refractory multiple myeloma receiving belantamab mafodotin in Europe. (A) The proportion of patients receiving ophthalmic examinations overall, based on oAEs and on eye disease history. (B) The proportion of patients reporting oAE with impact on daily living*

*A limitation of these analyses is the small number of patients analyzed. †Patients who experienced an oAE at any time during the period of belantamab mafodotin administration; the analysis did not link the timing of oAEs to the ocular examination. ‡Percentages are calculated based on the number of patients who received a second dose. §Percentages are calculated based on the number of patients who received a third dose. ‖Percentages are calculated based on the number of patients who received a fourth dose.

¶The impact of daily living was missing for 9 patients with keratopathy.

BCVA, best-corrected visual acuity; oAE, ocular adverse event.


A
Patients receiving ophthalmic exam, %
100
90
80
70
60
50
40
30
20
10
0
77.4
87.9
87.0
73.7
75.0
80.0
86.4
70.0
69.5
84.1
82.4
60.5
77.5
82.9
85.7
68.2
N=
84 58
23 57
76 55
22 50
59 44
17 38
40 35
14 22
Prior to belantamab mafodotin initiation
After dose 1 but before dose 2‡
After dose 2 but before dose 3§
After dose 3 but before dose 4‖
Ophthalmic examination period
Overall
oAE present at any time during follow-up period†
Eye disease history:
Ongoing
No history
B
% of patients
100
90
80
70
60
50
40
30
20
10
0
31.0
23.8
4.8
2.4
19.0
35.7
Eye irritation/ pain
Reading impairment
Driving impairment
Need for caregiver support
Other
No significant impact
Keratopathy¶ (n=42)

Supplementary Material

Supplementary Table 1. Select comorbidities present at belantamab mafodotin initiation

Comorbidity	Overall study population (N=84)
Any comorbidity of interest at belantamab mafodotin initiation, n (%)	51 (60.7)
Renal disease, n (%)	17 (20.2)
Pulmonary disease, n (%)	15 (17.9)
Cardiac disease, n (%)	33 (39.3)
Diabetes, n (%)	20 (23.8)
Eye disease, including history of dry eye/eye injuries affecting BCVA, n (%)	27 (32.1)*
Ongoing at belantamab mafodotin initiation	23 (27.4)
Ongoing eye disease of interest at belantamab mafodotin initiation†	
Cataracts	8 (9.5)
Dry eye	7 (8.3)
Keratopathy	4 (4.8)
Change in BCVA	1 (1.2)
Glaucoma	3 (3.6)
Blurred vision	2 (2.4)
Corneal erosion/defect	1 (1.2)
Eye irritation	1 (1.2)
Macular degeneration	1 (1.2)
Resolved at belantamab mafodotin initiation	4 (4.8)‡
Resolved eye disease of interest at belantamab mafodotin initiation§	
Cataracts	10 (11.9)
Keratopathy	2 (2.4)
Change in BCVA	5 (6.0)

Blurred vision	1 (1.2)
Ulcerative keratitis	1 (1.2)
Infective keratitis	1 (1.2)

*Type of eye disease was unknown for 1 of these patients. †Diabetic retinopathy was not considered an eye disease of interest. ‡Number of patients with all eye diseases resolved at belantamab mafodotin initiation. §Number of patients who had resolution of individual eye diseases at belantamab mafodotin initiation.

BCVA, best-corrected visual acuity.

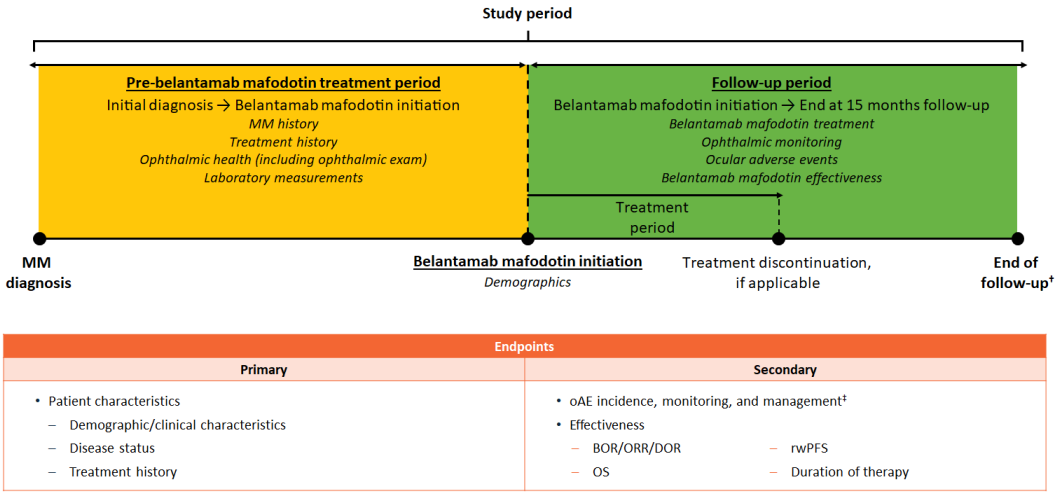
Supplementary Table 2. Ocular adverse events by presence or absence of ophthalmic disease history at belantamab mafodotin initiation

Patients with an oAE, n (%)	Ongoing ophthalmic disease (N=23)	Prior ophthalmic disease only (N=4)	No history of ophthalmic disease (N=57)
Keratopathy	14 (60.9)	2 (50.0)	26 (45.6)
Corneal erosions of defects	4 (17.4)	2 (50.0)	1 (1.8)
Blurred vision	2 (8.7)	1 (25.0)	3 (5.3)
Change in BCVA	2 (8.7)	0	2 (3.5)
Dry eye	0	0	1 (1.8)
Photophobia	1 (4.3)	0	0
Other oAE	5 (21.7)	1 (25.0)	10 (17.5)

BCVA, best-corrected visual acuity; oAE, ocular adverse event.

Supplementary Figure 1. Study design* (A) and patient disposition (B)

A



Endpoints	
Primary	**Secondary**
• Patient characteristics – Demographic/clinical characteristics – Disease status – Treatment history	• oAE incidence, monitoring, and management‡ • Effectiveness – BOR/ORR/DOR – OS – rwPFS – Duration of therapy

B

Enrolled: N=84

Country, n (%)
Italy: 32 (38.1)
Norway: 15 (17.9)
Austria: 14 (16.7)
Spain: 11 (13.1)
Belgium: 5 (6.0)
Germany: 4 (4.8)
Greece: 3 (3.6)

Received ≥1 belantamab mafodotin dose and had follow-up data, n (%): 84 (100)

Completed the study§ or died, n (%): 40 (47.6)
- Died‖, n (%): 27 (32.1)

Withdrew from the study (reasons other than death), n (%): 44 (52.4)
- Study terminated by sponsor: 39 (46.4)
- Withdrawal of consent: 1 (1.2)
- oAE: 0 (0)
- Other adverse event: 0 (0)
- Withdrawal by investigator: 0 (0)
- Lost to follow-up: 2 (2.4)
- Other: 2 (2.4)

Discontinued treatment, n (%): 59 (70.2)
- Disease progression: 28 (33.3)
- Death (unrelated to therapy): 13 (15.5)
- Reasons other than disease progression or death: 18 (21.4)
  - oAE: 7 (8.3)
  - Other adverse event: 2 (2.4)
  - Patient decision unrelated to adverse events: 2 (2.4)
  - End of treatment: 0 (0)
  - Other: 7 (8.3)

*Patients with RRMM who were due to receive their first dose of belantamab mafodotin in Europe, or who had initiated belantamab mafodotin within 3 months of enrolment were prospectively enrolled. Data prior to enrolment were collected retrospectively.

†End of follow-up at 15 months, study discontinuation for any reason, informed consent withdrawal or death, whichever came first; early closure of the study impacted study objectives requiring follow-up for

some patients.

[‡]Data were reported using both the NCI-CTCAE criteria and the KVA scale.[1] Missing data regarding ophthalmic exams may have resulted in underreporting of the exams.

[§]Patients who completed the planned 15 months of follow-up.

[‖]Deaths were recorded as due to disease/disease progression (n=18), AEs other than oAEs (n=2), unknown cause (n=5), and not listed (n=2).

AE, adverse event; oAE, ocular adverse event; MM, multiple myeloma.

References

1. European Medicines Agency. Blenrep. https://www.ema.europa.eu/en/medicines/human/EPAR/blenrep-0#:~:text=On%2022%20May%202025%2C%20the,relapsed%20or%20refractory%20multiple%20myeloma. Accessed August 18, 2025.