Belantamab mafodotin monotherapy for relapsed or refractory multiple myeloma: a real-world observational study in the United States

Belantamab mafodotin, a humanized, monoclonal antibody, conjugated to the microtubule inhibitor monomethyl auristatin F, binds to B-cell maturation antigen (BCMA) on plasma cells.[1] Accelerated approval as monotherapy was granted by the United States (US) Food and Drug Administration (FDA) in August 2020 for patients with relapsed/refractory multiple myeloma who have received at least four prior lines of therapy,[2,3] and conditional marketing authorization was granted by the European Medicines Agency (EMA).[4] The subsequent DREAMM-3 confirmatory study (NCT04162210) did not meet the primary endpoint of demonstrating superior progression-free survival compared to that achieved with pomalidomide and dexamethasone, resulting in US marketing authorization withdrawal in February 2023 and conditional marketing authorization non-renewal by the EMA in 2023.[4,5]

Studies assessing belantamab mafodotin in combination with standard-of-care treatments in second line and later for relapsed/refractory MM are ongoing.[6-8] Recent readouts of two phase III studies have demonstrated the potential of belantamab mafodotin combinations as new treatment options.[9,10] In DREAMM-7, belantamab mafodotin in combination with bortezomib and dexamethasone resulted in significantly longer progression-free survival (36.6 months, 95% confidence interval [95% CI]: 28.4 months - not reached [NR]) compared with daratumumab, bortezomib, and dexamethasone (13.4 months, 95% CI: 11.1-17.5 months) in patients who had received at least one prior line of therapy.[9] In DREAMM-8, belantamab mafodotin in combination with pomalidomide and dexamethasone conferred a significantly longer progression-free survival (NR, 95% CI: NR-NR) compared with pomalidomide, bortezomib, and dexamethasone (12.7 months, 95% CI: 9.1-18.5) in lenalidomide-exposed patients.[10]

During belantamab mafodotin approval for use in the US, patients underwent risk evaluation and mitigation strategy (REMS) ophthalmic monitoring.[11] With the evolving clinical program of belantamab mafodotin combinations, there is a need to understand how ocular events are managed in patients with relapsed/refractory MM who are treated with belantamab mafodotin in the real world. This retrospective, observational study evaluated the real-world treatment effectiveness and management of ocular events in patients with relapsed/refractory MM who received belantamab mafodotin.

This study complied with all applicable laws regarding patient privacy and used data from anonymized US electronic health records from the Flatiron Health database between January 1, 2011 and June 30, 2022. Due to the nature of the study, patient identification was not possible. Therefore, informed consent, ethics committee and institutional review board approval were not required. *Online Supplementary Figure S1A* depicts the study design, eligibility criteria, and endpoints.

Ocular events were categorized into keratopathy, blurred vision, dry eye, and keratitis. Eye examinations included best corrected visual acuity (BCVA) score assessments and slit lamp examinations. Keratopathy severity was classified as mild, moderate, or severe according to the first slit lamp examination occurring on or after the date of keratopathy onset, and the action taken after onset was reported for all patients with an ocular event.

Of 247 patients with MM, 184 were eligible for the study (*Online Supplementary Figure S1*B); their median age was 69.6 years, 46.7% were female, and 63.6% were White (*Online Supplementary Table S1*). Most patients were treated in a community setting (71.2%) and had an Eastern Cooperative Oncology Group performance status of 0-2 (84.8%). High-risk cytogenetics were reported in 39.7%, 87.0% had been exposed to triple-class therapy, and 82.1% were triple-class refractory. From initial MM diagnosis to treatment start, 67.9% of patients had ≥1 BCVA assessment. The patients' treatment history is shown in *Online Supplementary Table S1*.

The median (interquartile range) treatment period was 2.0 (1.1-4.5) months, with a follow-up of 4.1 (1.9-8.5) months. Treatment patterns and effectiveness are summarized in *Online Supplementary Table S2*. The median real-world overall survival was 7.9 months, and median real-world progression-free survival was 4.5 months.

During follow-up, 92 patients (50.0%) had ≥1 ocular event, with a median time from treatment initiation to first ocular event of 31.5 days and 2.0 administrations of belantamab mafodotin (Table 1). Multiple ocular events were reported in 48 patients (26.1%). The most common ocular events were keratopathy (41.3%), blurred vision (28.3%), dry eye (17.4%), and keratitis (9.8%).

A total of 76 (41.3%) patients had keratopathy events; six (3.3%) had multiple events, and 72 had ≥1 ocular examination on or after the first keratopathy onset date (Table 1). Keratopathy severity was determined for 62 patients, with mild, moderate, and severe keratopathy reported for 38 (20.7%), 19 (10.3%), and five (2.7%) patients, respectively (Table 2). Following a finding of keratopathy, 50 (27.2%) patients had action taken after the date of onset of the keratopathy.

When stratified by severity, action following keratopathy onset was taken in 27 of 38 patients with mild keratopathy, all 19 patients with moderate keratopathy, and four of five patients with severe keratopathy (Table 2). Therapy holds occurred in

19 patients (10.3%) with mild keratopathy, 15 patients (8.2%) with moderate keratopathy, and four patients (2.2%) with severe keratopathy (Table 2). After therapy holds, belantamab mafodotin was subsequently administered to 17 of 38 patients with mild keratopathy, 12 of 19 with moderate keratopathy, and two of five with severe keratopathy; the median time to subsequent administration was shorter for cases of mild keratopathy (21.0 days) than for moderate (59.5 days) and severe (46.0 days) forms (Table 2).

Dose or schedule changes were also used to manage keratopathy (Table 2). Belantamab mafodotin was discontinued in three of 38, four of 19, and one of five patients with mild, moderate, and severe keratopathy, respectively (Table 2), equating to keratopathy-related discontinuation in eight patients (4.3%). Overall, the frequency of eye examinations in the real world was generally high prior to the first two visits, with 169 patients (91.8%) having ≥1 recorded ophthalmic examination before the start of treatment, of which 164 (89.1%) were within 28

Table 1. Assessment of ocular events during follow-up

Ocular events	Patients N=184
Follow up time in months, median (mean ± SD)	4.1 (5.6±4.8)
N of events, median (mean ± SD)	0.5 (0.9±1.1)
Patients with ≥1 event, N (%)	92 (50.0)
Time from start of treatment to first event in days, median (mean ± SD)	31.5 (39.4±31.6)
N of belantamab mafodotin administrations prior to first event, median (mean ± SD)	2.0 (2.1±1.1)
By number of belantamab mafodotin administrations prior to first event, N (%)	
1	30 (16.3)
2	40 (21.7)
≥3	22 (12.0)
N of events in patients with ≥1 event, median (mean ± SD)	2.0 (1.7±0.9)
By number of events, N (%)	
1	44 (23.9)
>1	48 (26.1)
2	34 (18.5)
≥3	14 (7.6)
Type of event, N (%)	
Keratopathy	76 (41.3)
Patients with multiple keratopathy events	6 (7.9)
Keratopathy severity of first event	
Patients with ≥1 ocular examination on or after the keratopathy onset date	72 (94.7)
BCVA score assessment	63 (82.9)
Slit lamp examination	71 (93.4)
Blurred vision	52 (28.3)
Dry eye	32 (17.4)
Keratitis	18 (9.8)
Action taken	
Therapy hold*, N (%)	57 (31.0)
Patients subsequently administered belantamab mafodotin, N (%)	41 (22.3)
Time from last administration before the onset date to subsequent administration† in days, median (mean ± SD)	42.0 (48.4±27.2)
Hold >28 days, N (%)	26 (14.1)
Treatment for adverse event, N (%)	55 (29.9)
Therapy dose or schedule change, N (%)	18 (9.8)
None, N (%)	14 (7.6)
Therapy discontinuation, N (%)	13 (7.1)

Follow-up was defined as the period between the first belantamab mafodotin administration (start of treatment) and start of participation in a clinical trial, date of last recorded clinical interaction, end of data availability, or death, whichever occurred first. *Defined as any treatment within the given line of therapy that was held or delayed as a result of the adverse event, defined as a gap of ≥28 days and <90 days from the previous to the subsequent belantamab mafodotin administration. Therapy holds were dissociated from the timing of belantamab mafodotin administrations; †Reported over all therapy holds to account for patients with multiple therapy holds. N: number; SD: standard deviation; BCVA: best corrected visual acuity.

days before the first administration. For 142 patients with ≥2 belantamab mafodotin administrations (77.2%), 131 had ≥1 ophthalmic examination between the first and second administration (71.2% overall) (Table 3), all within 28 days of the first administration. The median ratio of ophthalmic visits to belantamab mafodotin administrations was 1.0. The median BCVA score (logMAR, Snellen equivalent [feet]) was similar between patients with ≥1 ophthalmic examination (0.0, 20/20; N=135) or with ≥2 ophthalmic examinations (0.0, 20/20; N=98) during the follow-up period (Table 3).

An ophthalmic examination was performed within 14 days of worsening symptoms in 59 of 76 patients with keratopathy (77.6%). Subsequent ophthalmic examinations were performed in 56 patients (73.7%), with keratopathy reported as mild, moderate, and severe in 33 (17.9% overall), 20 (10.9% overall), and five (2.7% overall) patients, respectively (Table 3). Over the treatment period, ocular treatments were received by 85.3% of patients. Preservative-free artificial tears (70.7% of patients) followed by eye drops (18.5%) were the most frequent ocular treatments used in the overall population (Table 3).

Ocular events were observed in half of patients in this study, which is lower than the ocular adverse event rates reported in the DREAMM-2 and DREAMM-3 trials (66-74%).[12,13] Ocular events that were not systematically captured in the electronic health records, as well as the shorter follow-up period for this study (median 4.1 months compared with ~3 years and 11.5 months in DREAMM-2 and DREAMM-3, respectively)[12,13] may have contributed to the lower event rate observed. Keratopathy was the most common ocular event reported in patients receiving belantamab mafodotin, with more cases of mild keratopathy reported than moderate or severe cases combined.

Ocular events were effectively managed through dose modifications with minimal treatment discontinuation. Our findings highlight that belantamab mafodotin-related ocular events are manageable in the real world. Temporary therapy hold was the most frequent action taken for ocular events. When stratified by keratopathy severity, 40-63% of patients had a subsequent belantamab mafodotin dose following a dose hold due to keratopathy, highlighting the transient nature of the holds for a sizeable proportion of patients. These findings highlight that ocular events associated with belantamab mafodotin can be effectively managed in real-world academic and community settings as well as in clinical trials.[9,10]

This study should be interpreted within the context of some of the limitations common to real-world studies. First, in contrast to the stringent evaluation criteria applied to clinical trials, outcomes assessed retrospectively in real-world studies may vary across physicians and between patients due to subjective assessment and reporting. Furthermore, less rigorous real-world monitoring may have led to delayed or under-identification of toxicity or disease progression. Second, as patients may have been treated at multiple practices, events and eye examinations may not have been systematically captured in the electronic health records available. Data from electronic health records may have been subject to coding error and misclassification, which may have led to misrepresentation of events. Third, ocular events reported in the data may not be all the events experienced by patients receiving belantamab mafodotin, as data were only abstracted for prespecified events. Fourth, patients were excluded from this study if they had participated in a clinical trial; including a wider range of patients may have could include the generalizability of the data. Fifth, the Flatiron Health database does not include all US oncology centers and may not be representative of the broader US population of patients with relapsed/refractory MM. Lastly, the withdrawal of belantamab mafodotin from

Table 2. Assessment and management of keratopathy events during follow-up, stratified by keratopathy severity by slit lamp examination findings.

Keratopathy severity, N=62	Mild N=38	Moderate N=19	Severe N=5
Patients with action taken following keratopathy onset, N (%)	27 (71.1)	19 (100.0)	4 (80.0)
Therapy hold,* N (%)	19 (50.0)	15 (78.9)	4 (80.0)
Patients with subsequent belantamab mafodotin administration, N (%)	17 (44.7)	12 (63.2)	2 (40.0)
Time from last administration before the onset date to subsequent administration in days, median (mean ± SD)	21.0 (34.7±26.8)	59.5 (64.4±29.8)	46.0 (46.0±5.7)
Hold >28 days, N (%)	5 (13.2)	10 (52.6)	2 (40.0)
Treatment for event, N (%)	19 (50.0)	11 (57.9)	1 (20.0)
Therapy dose or schedule change, N (%)	7 (18.4)	6 (31.6)	1 (20.0)
Therapy discontinuation, N (%)	3 (7.9)	4 (21.1)	1 (20.0)

Follow-up was defined as the period between the first belantamab mafodotin administration (start of treatment) and start of participation in a clinical trial, date of last recorded clinical interaction, end of data availability, or death, whichever occurred first. *Defined as any treatment within the given line of treatment that was held or delayed as a result of the adverse event, defined as a gap of ≥28 days and <90 days from the previous to the subsequent belantamab mafodotin administration. Therapy holds were dissociated from the timing of belantamab mafodotin administrations. N: number; SD: standard deviation.

Table 3. Ophthalmic monitoring during follow-up.

Ophthalmic examinations before each belantamab mafodotin administration	Patients N=184
Median ratio of ophthalmic visits to administration	1.0
First administration Patients with ≥1 ophthalmic examination before first administration, N (%) ≤14 days prior to administration, N (%) ≤28 days prior to administration, N (%)	 169 (91.8) 142 (77.2) 164 (89.1)
Second administration Patients with ≥2 administrations, N (%) Patients with ≥1 ophthalmic examination between first and second administration, N (%) ≤14 days prior to administration, N (%) ≤28 days prior to administration, N (%)	 142 (77.2) 131 (71.2) 126 (68.5) 131 (71.2)
Median BCVA score Patients with ≥1 ophthalmic examination; N=135, logMAR, Snellen equivalent (feet) Patients with ≥2 ophthalmic examinations; N=98, logMAR, Snellen equivalent (feet)	 0.0, 20/20 0.0, 20/20
Ophthalmic examination within 14 days of worsening keratopathy symptoms; N=76, N (%)	59 (77.6)
Subsequent ophthalmic examinations in patients with keratopathy; N=76, N (%) Keratopathy severity, N Mild Moderate Severe	56 (73.7) 33 20 5
Ocular treatments, N (%) Any Preservative-free artificial tears Eye drops Other	 157 (85.3) 130 (70.7) 34 (18.5) 16 (8.7)

Follow-up was defined as the period between the first belantamab mafodotin administration (start of treatment) and start of participation in a clinical trial, date of last recorded clinical interaction, end of data availability, or death, whichever occurred first. N: number; BCVA: best corrected visual acuity.

the US market attenuated new patients initiating treatment after February 2023.

This study provides insight into ocular event management following belantamab mafodotin treatment in real-world settings and highlights effectiveness in patients with relapsed/refractory MM. These findings support ongoing studies of belantamab mafodotin in combination therapies and provide important insights into ocular event management, as well as the benefits and risks associated with the use of belantamab mafodotin in the real world.

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Contributions

MH, DK, RV, FE, MD, NK, JB, NB, LCO, GG, AU, MM, MSD, FL, MC and HCL contributed to the conception or design of the study, data analysis, and data interpretation. LPH contributed to data analysis and interpretation.

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Data-sharing statement

The datasets generated and/or analyzed during the current study are not publicly available due to the proprietary nature of the electronic health records. The protocol and study report may be available from the corresponding author on reasonable request.

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