Belantamab Mafodotin (Belamaf) for Relapsed/Refractory Multiple Myeloma (RRMM): A Real-World Observational Study

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Introduction

Belantamab mafodotin (belamaf) is a first-in-class B-cell maturation antigen-targeting antibody-drug conjugate (ADC) approved for the treatment of patients with relapsed or refractory multiple myeloma (RRMM) who have received ≥4 prior therapies, including an anti-CD38 monoclonal antibody (mAb), a proteasome inhibitor (PI), and an immunomodulatory agent.[1,2]

In the pivotal Phase II DREAMM-2 study (NCT03525678; final analysis to be presented at ASH; poster 3246),[3] single-agent belamaf demonstrated effectiveness and had a manageable safety profile in patients with RRMM.[4,5]

Due to the occurrence of ocular events in DREAMM-2, eye examinations by an eye care professional are required prior to first belamaf administration, before each belamaf dose, and as clinically indicated during treatment in the US.[4,5]

This is the first study to report on the real-world use of belamaf in patients with RRMM and the occurrence of ocular events in routine clinical practice in the USA using national electronic medical records.

Objective

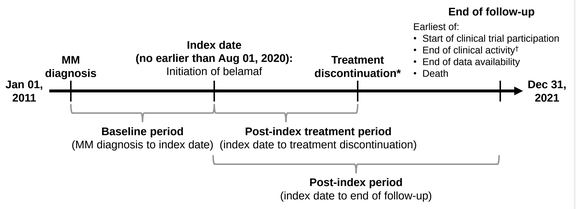
To characterize patients with RRMM, including triple-class-refractory patients, treated with belamaf in the US to better understand the real-world management of these patients, including the occurrence and management of ocular symptoms, as well as the effectiveness of belamaf in the real world.

Methods

This retrospective, longitudinal, observational study, analyzed de-identified US electronic health record data derived from the Flatiron Health Database from 01/01/2011 to 12/31/2021, that extracted data on belamaf dosing, derived response, ocular exams, and AESI from unstructured fields of patient charts. The Flatiron Health database is a longitudinal database, comprising de-identified patient-level structured and unstructured data, curated via technology-enabled abstraction.[6]

Eligible patients had a confirmed MM diagnosis, ≥1 record of belamaf administration (after August 01, 2020), were ≥18 years of age on the index date, and had available chart abstraction data for ocular safety and effectiveness outcomes of interest. Patients who participated in an interventional clinical trial during the baseline period or on the index date were excluded (**Figure 1**).

Figure 1. Study design



*Treatment discontinuation was defined as the earliest of the permanent discontinuation of belamaf treatment (as recorded clinician decision), the confirmed date of a new line of treatment, or the date of the end of follow-up; †Clinical activity was defined from the date of the first recorded interaction to the date of the last recorded interaction, where a recorded interaction between the patient and a healthcare provider included visits, use of therapies or lab tests, vital assessments, ECOG assessments, or comorbidity diagnoses

Demographic characteristics were evaluated on the index date; disease characteristics and treatment history were described during the baseline period.

Belamaf treatment patterns, ophthalmic monitoring, and ocular AESI were included during the post-index treatment period, unless otherwise specified.

Patients with ocular AESI were included using pre-specified terms for belamaf-related ocular AESI (including keratopathy, blurred vision, dry eye, and keratitis) abstracted from patient charts.

Frequency/timing of ophthalmic monitoring visits, duration of belamaf treatment, reasons for belamaf discontinuation, and clinical effectiveness of belamaf (i.e., ORR*, overall survival [OS], and progression-free survival [PFS]) were assessed during the post-index period.

Ocular AE severity was defined as mild, moderate, or severe based on the first slit lamp examination occurring on or after the AE onset date during the post-index period.

Ocular AESI information for patients with ≥4 months of follow-up is presented separately, as follow-up time was too short to evaluate the incidence of ocular AESI and associated treatment mitigations for patients receiving their first dose of belamaf close to the data cut-off date.

*ORR was comprised of PR and VGPR. Flatiron uses International Myeloma Working Group criteria to derive PR (defined as ≥50% reduction of serum M-protein, reduction in 24h UPEP by ≥90% or to <200 mg/24h, or if serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved free light chain level) and VGPR (defined as serum M-protein not detectable on electrophoresis serum test or 24h UPEP not detectable on electrophoresis urine.

Results

Patient characteristics

A total of 186 patients with a confirmed MM diagnosis and who received ≥1 administration of belamaf were identified, of which 49 were excluded due to participation in an interventional clinical trial (during the baseline period or on the index date) or lack of chart abstraction data.

Overall, 137 patients were included in the study (**Table 1**).

- Mean age was 67.9 years and 50.4% of patients were female.
- Median (interquartile range [IQR]) time between MM diagnosis and index date was 4.8 (3.0–6.7) years, median (IQR) number of lines of therapy (LOTs) prior to belamaf initiation was 5.0 (4.0–7.0), 64.2% received at least 5 LOTs prior, and 76.6% were triple-class refractory.
- A total of 107 (78.1%) patients had ≥1 BCVA score assessment (Snellen test or equivalent) during the baseline period or on the index date.
- Median follow-up in the post-index period was 3.1 months.

Table 1. Patient demographics, disease characteristics, and treatment history between MM diagnosis and belamaf initiation

Characteristic	N=137
Patient demographics	
Age, years, mean (± SD)	67.9 (± 10.0)
Gender, n (%)	
Female	69 (50.4)
Male	68 (49.6)
Race, n (%)	
White	87 (63.5)
Black or African American	17 (12.4)
Other*	9 (6.6)
Unknown	24 (17.5)
Disease characteristics	
Extramedullary disease, n (%)	36 (26.3)
ISS stage n (%)	
I	29 (21.2)
II	28 (20.4)
III	39 (28.5)
Unknown	41 (29.9)
Cytogenetic risk, n (%)†	
High	62 (45.3)
Standard	55 (40.1)
Unknown	20 (14.6)
Pre-existing comorbidities‡	
Cardiovascular disease	73 (53.3)
Renal disease	52 (38.0)
Bone disease	44 (32.1)
Cardiac disease	33 (24.1)
Peripheral neuropathy	30 (21.9)
Pulmonary disease	27 (19.7)
Eye disease	22 (16.1)
Diabetes	19 (13.9)
Refractory status	
Triple-class§	105 (76.6)
Quad¶	41 (29.9)
Penta**	40 (29.2)
Number of previous LOTs, n (%)††	
1	3 (2.2)
2	7 (5.1)
3	11 (8.0)
4	28 (20.4)
5	34 (24.8)
6	17 (12.4)
7	15 (10.9)
8+	22 (16.1)
Progression on the last LOT prior to belamaf initiation, n (%)	47 (34.3)

*Number of patients in each race subgroup categorized was too low to be reported separately without risking de-identification of patients; †High-risk cytogenetics were defined as presence of del[17p], t[4;14], t[14;16], t[14;20], or 1q21 gains/amplifications identified by FISH or karyotyping. Standard-risk cytogenetics were defined as evidence of genetic testing but no documented presence of high-risk identifiers; ‡Comorbidities limited to those occurring in >10% of patients; §Triple-class-refractory MM was defined as MM that does not respond to treatment with any of the following drug classes: immunomodulatory agent (lenalidomide, pomalidomide, thalidomide), PI (bortezomib, carfilzomib, ixazomib), mAb (daratumumab, isatuximab); ¶Quad-refractory MM was defined as MM that does not respond to treatment to bortezomib, carfilzomib, lenalidomide, or pomalidomide; **Penta-refractory MM was defined as MM that does not respond to treatment with bortezomib, carfilzomib, lenalidomide, pomalidomide, or daratumumab; ††LOT was oncologist-defined by the rule-based Flatiron Health algorithm specific to MM

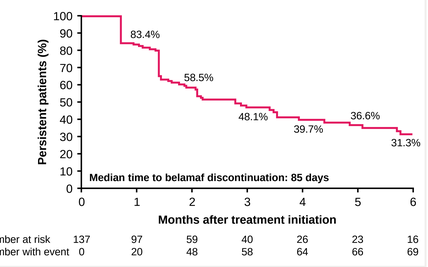
Persistence on belamaf

Median (IQR) treatment period was 1.4 (0.7–3.3) months and the median (IQR) follow-up time was 3.1 (1.4–6.0) months.

At 3- and 6-months after starting therapy, 48.1% and 31.3% of patients, respectively, were still on treatment with belamaf (**Figure 2**).

Reason for discontinuation was reported for 71 patients; the most common reasons listed were disease progression (33.8%), and treatment toxicity (19.7%), or both (15.5%).

Figure 2. Proportion of patients who continued on belamaf



Ocular AESI

In total, 92.7% of patients had a record for an ophthalmic examination prior to the first administration of belamaf.

Among patients with ≥4 months of follow-up (57 patients), 71.9% had at least 1 ocular AESI, with keratopathy and blurred vision being the most frequent types (both 52.6%) (**Table 2**).

Mean (SD) time to first ocular AESI was 44.7 (40.2) days, with a mean (SD) of 2.3 (1.3) belamaf doses prior to first ocular AESI.

Among patients with a keratopathy event, ≥4 months of follow-up, and severity information (n=25), 48.0% had mild and 52.0% had moderate/severe keratopathy.

- Most ocular AESI (58.5%), including keratopathy events (76.0%), were managed by therapy hold (**Table 3**).

Table 2. Occurrence of ocular AESI during post-index period

	Post-index period* (N=137)	Patients with ≥4 months of post-index period (n=57)
Patients with ≥1 ocular AESI, n (%)	**(n=71; 51.8)**	**(n=41; 71.9)**
Time to first ocular AESI, days, mean ± SD	39.1 (± 33.6)	44.7 (± 40.2)
Number of belamaf administrations prior to first ocular AESI, mean ± SD	2.1 (± 1.2)	2.3 (± 1.3)
Number of ocular AESI, mean ± SD	1.8 (± 0.8)	1.4 (± 1.2)
1 ocular AESI, n (%)	30 (21.9)	13 (22.8)
2 ocular AESI, n (%)	32 (23.4)	21 (36.8)
≥3 ocular AESI, n (%)	9 (6.6)	7 (12.3)
Type of ocular AESI, n (%)		
Keratopathy	56 (40.9)	30 (52.6)
Blurred vision	44 (32.1)	30 (52.6)
Dry eye	27 (19.7)	18 (31.6)
Keratitis	17 (12.4)	12 (21.1)
Patients with ≥1 keratopathy event, n (%)	56 (40.9)	30 (52.6)
Patients with ≥1 ocular exam on or following the first keratopathy event during the post-index period, n (%)	53 (94.6)	29 (96.7)
BCVA score assessment	45 (84.9)	23 (79.3)
Slit lamp examination	52 (98.1)	29 (100.0)
Mild keratopathy	27 (61.4)	12 (48.0)
Moderate/severe keratopathy	17 (38.6)	13 (52.0)

*The post-index period is defined as the period from the index date to the end of follow-up (i.e., start of participation in a clinical trial, end of clinical activity, end of data availability, or death)

Table 3. Assessment and management of keratopathy events during the post-index period

	Patients with keratopathy event (n=56)	Patients with keratopathy event and ≥4 months of follow-up (n=30)
Patients with ≥1 ocular exam on keratopathy onset date or following the keratopathy event during the post-index period, n (%)	53 (94.6)	29 (96.7)
Severity of first keratopathy* event (among patients with keratopathy severity information), n (%)†	**(n=44)**	**(n=25)**
Mild	27 (61.4)	12 (48.0)
Action taken, n (%)‡	19 (70.4)	8 (66.7)
Therapy hold§	12 (63.2)	5 (62.5)
Patients with subsequent belamaf administration	9 (75.0)	4 (80.0)
Patients with therapy hold >28 days	2 (22.0)	1 (25.0)
Treatment for ocular AESI¶	10 (52.6)	5 (62.5)
Therapy dose or schedule change**	7 (36.8)	2 (25.0)
Therapy discontinuation	2 (10.5)	2 (25.0)
Moderate/severe††	17 (38.6)	13 (52.0)
Action taken, n (%)‡	17 (100)	13 (100)
Therapy hold§	15 (88.2)	11 (84.6)
Patients with subsequent belamaf administration	10 (66.7)	9 (81.8)
Patients with therapy hold >28 days	9 (90.0)	9 (100)
Treatment for ocular AESI¶	9 (52.9)	8 (61.5)
Therapy dose or schedule change**	3 (17.6)	3 (23.1)
Therapy discontinuation	3 (17.6)	2 (15.4)

*Keratopathy severity is based on slit lamp exam findings closest to the keratopathy onset date; †Of the 56 patients with keratopathy in the full cohort and the 30 patients in the cohort with ≥4 months of follow-up, there were 12 and 5 patients without severity information recorded, respectively; ‡Patients may have had multiple actions taken following the keratopathy event, therefore the categories presented are not mutually exclusive; §Defined as any treatment hold or delay as a result of an AE; ¶Treatment for the AE is defined as any treatment (does not have to be pharmacological) that is recommended, prescribed, or administered by the clinician to treat the AE; **Defined as dose modifications to the given LOT as a result of the AE or if the AE caused a change in treatment schedule; ††Number of patients with severe keratopathy was too low to be reported separately without risking de-identification of patients

Effectiveness

Thirty patients achieved a response (ORR at 6 months: 30.2%). Of those with an overall response, 27 (90%) achieved a PR and 3 (10%) achieved a VGPR.

Median real-world PFS and OS were 5.4 months and 7.8 months, respectively (**Figure 3**).

Limitations

Unlike clinical trial settings, the assessment of outcomes in real-world clinical practice may not be consistent across patients or across physicians. Specifically, it is not possible to implement consistent monitoring and apply homogenous evaluation criteria that are inherent to clinical trial design.

Excluding patients who have participated in clinical studies could potentially confound the data and may have resulted in low patient numbers for inclusion, especially in academic settings. Additionally, the Flatiron Health Database is not comprehensive of all US oncology centers.

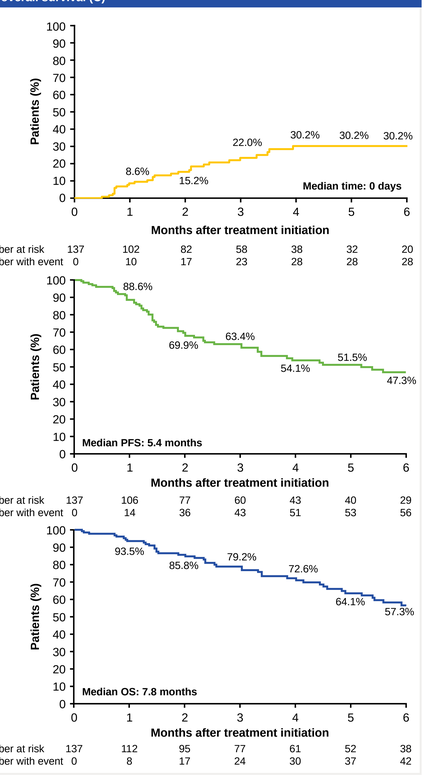
Ophthalmic monitoring may be underreported, as patients may seek care at different practices or hospitals, which may not always be captured in the Flatiron Health Database.

Outcome measures such as treatment response are clinician-assessed in the real-world setting and may differ from the prespecified definitions used in clinical trials, complicating comparisons between clinical trials and real-world data.

Short observation periods and small sample size limit the generalizability of findings.

Data are from patient charts. Specific events, such as details of comorbid conditions, including ophthalmic history, may be missing, and inconsistencies may occur between charts.

Figure 3. Real-world time to overall response (A), progression-free survival (B), and overall survival (C)



Conclusions

These findings provide important insights into the real-world use of belamaf in patients with RRMM. Patients in this study were heavily pre-treated with multiple comorbidities and belamaf can help fill the unmet treatment need.

Compared with the belamaf 2.5 mg/kg cohort in DREAMM-2, patients in this study were slightly older, had fewer prior LOTs, and had a shorter time between MM diagnosis and belamaf treatment initiation.[4]

ORR in this real-world study was also consistent with the DREAMM-2 study (30.2% vs 32%); however, PFS was longer (5.4 vs 2.8 months) and OS shorter (7.8 vs 13.7 months) than in DREAMM-2.[5]

Keratopathy was one of the most common ocular AESI reported in patients receiving belamaf treatment (40.9%).[4]

Overall, patients with RRMM treated with belamaf in the clinical real-world setting experienced similar outcomes to those who received belamaf in the DREAMM-2 study,[4] including therapy holds to address ocular AESI. Ocular events were managed by HCPs, and patients were remaining on treatment.

Abbreviations

ADC, antibody-drug conjugate; AE, adverse event; AESI, adverse event(s) of special interest; BCVA, best corrected visual acuity; belamaf, belantamab mafodotin; ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; HCP, healthcare professional; IQR, interquartile range; ISS, International Staging System; LOT, line of therapy; mAb, monoclonal antibody; MM, multiple myeloma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; PR, partial response; RRMM, relapsed or refractory multiple myeloma; SD, standard deviation; UPEP, urine protein electrophoresis; VGPR, very good partial response

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