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ORIGINAL RESEARCH

Real-World Outcomes of Belantamab Mafodotin for Relapsed/Refractory Multiple Myeloma (RRMM): Preliminary Results of a Spanish Expanded Access Program (EAP)

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ABSTRACT

Introduction: Belantamab mafodotin (BM) is a new anti-BCMA antibody–drug conjugate, recently approved for triple-class relapsed and refractory multiple myeloma (RRMM). We assessed real-world outcomes with BM in patients under the Spanish Expanded Access Program (EAP).

Methods: We conducted an observational, retrospective, multicenter study including RRMM patients who received ≥ 1 dose of BM (Nov 2019 to Jun 2021). The primary endpoint was overall response rate (ORR). Secondary

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endpoints were progression-free survival (PFS), overall survival (OS), and incidence of treatment-emergent adverse events (TEAEs).
Results: Thirty-three patients were included with a median of 70 years of age (range, 46–79 years). Median time from diagnosis was 71 months (range, 10–858 months). Median prior lines was 5 (range, 3–8 lines); 90% of patients were triple-/quad-/penta-refractory; 48% showed high-risk cytogenetics. Median BM doses was 3 (range 1–16 doses), with a median follow-up of 11 months (6–15 months). ORR was 42.2% (≥ VGPR, 18.2%).Median PFS was 3 months (95% CI 0.92–5.08) in the overall population, and 11 months (HR 0.26; 95% CI 0.10–0.68) for patients who achieved ≥ PR. PFS was not significantly different according to age, cytogenetic risk, and prior therapy lines. OS was 424 days (95% CI 107–740). Non-hematological TEAEs (57.6% of patients; 30.3% ≥ G3) included keratopathy (51.5%; 21.2% ≥ G3) and patient-reported vision-related symptoms (45.5%). Keratopathy was resolved in 70.6% of patients. G3 hematological TEAEs was 18.2%, thrombocytopenia (21.2%). Dose reductions due to TEAEs: 30.3%; delays: 36.4%. Treatment discontinuation causes: progression (54.5%), toxicity (non-ocular; 6%/ocular; 6% /ocular + non-ocular toxicity; 3%), death (6%), and patient's decision (3%).
Conclusions: BM showed relevant anti-myeloma activity in RRMM with a manageable safety profile. These results corroborate those observed in the BM pivotal trial.

Keywords: Triple-class relapsed and refractory multiple myeloma; Belantamab mafodotin; Real-world outcomes; Effectiveness; Safety

Key Summary Points

Therapeutic options for triple-class refractory/relapsed multiple myeloma (RRMM) patients are limited.

Belantamab mafodotin (BM) is a new anti-BCMA antibody–drug conjugate recently approved for this indication for which real-life evidence needs to be evaluated.

Our real-world experience of BM in triple-class RRMM (Spanish Expanded Access Program [EAP]) appears to be consistent with those observed in the pivotal DREAMM-2 study (efficacy and safety).

Adequate measures to successfully prevent and mitigate ocular toxicity are necessary and should be adopted to prevent major ocular toxicity to avoid permanent discontinuation of BM treatment, compromising clinical results.

INTRODUCTION

Multiple myeloma (MM) is a hematologic malignancy of terminally differentiated plasma cells (PCs) that currently remains incurable for most patients [1–4]. Multiple novel treatment options have been introduced over the last two decades, such as proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and anti-CD38 (an antigen on the PCs surface) monoclonal antibodies (mAbs) [1, 3, 5]. These pharmacological advances, together with new and more effective strategies (combinations, maintenance, etc.), have led to better outcomes and improved survival [6–8]. However, most MM patients eventually relapse despite responding to the first-line of treatment [4, 9]. After relapsing, the duration of responses to further treatments becomes shorter and shorter, and eventually patients develop drug resistance (refractoriness) [3, 10].

Patients who are refractory to the standard drug classes (PIs, IMiDs, and anti-CD38 mAbs), otherwise known as triple-class refractory MM, have a poor prognosis (limited overall survival [OS] and progression-free survival [PFS] outcomes), with an estimated OS of less than 1 year [3, 5]. Therapeutic options for both triple-class refractory [5] and refractory MM patients who were triple-class exposed [11] are limited, representing a population with a fairly clear unmet medical need [3].

All this reflects the need for more effective therapies with a novel mechanism of action. The B-cell maturation antigen (BCMA),

expressed exclusively in mature B cells and PCs, represents an attractive target for the treatment of MM in recent years [1, 3]. It has been included in various therapeutic approaches such as chimeric antigen receptor-modified T cells (CAR-Ts), bispecific antibody (bsAb) construct, and antibody–drug conjugates (ADCs) [3, 4].

Belantamab mafodotin (BM) is the first-in-class ADC in MM that utilizes a humanized anti-BCMA mAb linked to the microtubule-disrupting agent monomethyl auristatin F (MMAF) [12]. It has been recently approved by the FDA and EMA as monotherapy for triple-class refractory MM patients that have previously received four or more therapies [2, 4, 13], including at least one PI, one IMiD, and one anti-CD38 mAb.

The evidence for its approval comes from the randomized phase 2 DREAMM-2 trial, with favorable results (overall rate response [ORR] of 30% and a median of OS of 13.7 months at a 13-month follow-up) [12, 14–16].

It is essential to assess BM treatment data in routine practice to rule out the potential discrepancies between clinical trial efficacy (ideal circumstances and selected patients) and real-world effectiveness [7] and thus be able to corroborate its true benefit. Additionally, this data would increase knowledge on the appropriate treatment management to obtain the maximum benefit for patients. Therefore, the real-world data from those patients unable to participate in a clinical trial but that have received BM under the US Expanded Access Program (EAP; NCT03763370), or the expanded access compassionate care program in Europe, are being analyzed. However, little data has yet been published [12, 17–22], mainly from scientific meetings.

Considering the above and the forthcoming availability of BM in the Spanish National Healthcare System, this study aimed to assess the efficacy and safety of BM treatment administered via the Expanded Access compassionate care Program (EAP) [23] for triple-class exposed RRMM patients. We present preliminary results of the Spanish population included in this EAP of BM.

METHODS

An observational, retrospective, multicenter study was carried out by the Madrid Group of Monoclonal Gammopathies (GM-GM, by its Spanish acronym) in the 14 hospitals belonging to the Haematology and Haemotherapy Madrid Association (AMHH, by its Spanish acronym). All procedures in this study met the bioethical standards outlined in the Helsinki Declaration [24]. It was approved by the local ethics committee (Hospital Universitario Ramón y Cajal) and all patients provided written informed consent.

The study was performed by retrospectively collecting data from all patients who had received at least one dose of BM as a single agent (2.5 mg/kg intravenous [IV] every 3 weeks [Q3W]) under the EAP in the region of Madrid (Spain). This EAP was effective in Spain from November 2019 to June 2021. The EAP eligibility criteria for BM were: RRMM with $\geq$ 4 prior therapies and refractory to anti-CD38, IMiD, and PI, progression on last therapy, absence of satisfactory alternative standard of care regimen, and no eligibility for any ongoing BM clinical trial.

Patients were enrolled from February 2020 until May 2021. During this period, participating investigators of the hematology centers provided data from the medical records and entered them in a case report form distributed to the sites. Data included demographics, time from diagnosis, baseline disease characteristics, prior therapies, BM treatment (dose, dose delays/reductions, etc.), response to BM, time of follow-up, and adverse events (AEs) related to BM therapy. High-risk cytogenetics was defined as del17q, t(4;14), t(14;16), and 1q21+.

The primary endpoint was overall response rate (ORR), defined as partial response (PR) or better. Secondary endpoints were: PFS, defined as the time from the first day of BM administration to progression or death; OS, defined as the time from the first administration of BM to death from any cause, and the incidence of treatment-emergent AEs (TEAEs) (CTCAE V5) [25], with a major focus on ocular and

hematologic toxicities according to the keratopathy and visual acuity (KVA) scale [15].

The clinical benefit rate (CBR) was considered as the percentage of patients that had a response higher or equal to minimal response (≥ MR). Categorical variables were described by numbers and percentages, and continuous variables were described by medians, interquartile range (IQR), and 95% confidence intervals (CI).

The proportion of patients achieving an overall response according to different baseline characteristic subgroups was analyzed; patients with unknown or missing response data were treated as non-responders.

For the analysis of both survival variables (PFS and OS), the Kaplan–Meier method (SPSS 23.0 software package [SPSS Inc., Chicago, IL, USA]) was used. Both variables were also analyzed according to the response in a post hoc analysis. Additionally, the PFS according to different baseline characteristic subgroups was analyzed.

RESULTS

Baseline Characteristics

A total of 33 patients from 14 different centers were included in the study. They were all that were included in the EAP in these centers. Table 1 shows the patients and disease characteristics and the information of the prior treatments at EAP inclusion.

Patients entered the EAP at a median of 5.9 years from diagnosis (range, 3.9–8.2). The median age of patients at EAP inclusion was 70 years (range, 58–72 years), and 18 patients (54.0%) were women. High-risk cytogenetic features were shown in 16 of 33 patients (48.4%). Twenty-five patients (76%) underwent prior autologous stem cell transplantation (ASCT).

The median number of prior therapy lines was 5 (range, 3–8), with 27.0% (9/33) of patients being triple-refractory, 30.0% (10/33) quad-refractory, and 33% (11/33) penta-refractory. None of the patients had received prior anti-BCMA therapy.

Table 1 Characteristics of study population (n = 33) and disease at EAP inclusion and information of prior treatment

	EAP (n = 33)
Patient characteristics	
Age, median (IQR), years	70 (58–72)
18–64	14 (42%)
65–74	15 (46%)
≥ 75	4 (12%)
Sex	
Male	15 (46%)
Female	18 (54%)
Disease characteristics	
Time from diagnosis, median (IQR), years	5.92 (3.88–8.21)
ISS stage; n (%)	
ISS I	14 (42%)
ISS II	5 (15%)
ISS III	9 (28%)
Unknown	5 (15%)
High-risk cytogenetics; n (%)	
del17p	2 (6%)
t(4;14)	4 (12%)
t(14;16)	0 (0%)
1q21+	10 (30%)
Type of MM; n (%)	
IgG	20 (61%)
Non-IgG or unknown	13 (39%)
Extramedullary disease, n (%)	13 (39%)
Refractory status; n (%)	
Triple-refractory	9 (27%)
Quad-refractory	10 (30%)
Penta-refractory	11 (33%)
Prior treatments	

Table 1 continued

	EAP (n = 33)
Prior lines of therapy, median (range)	5 (3–8)
≤ 4 lines	14 (42%)
> 4 lines	19 (58%)
Previous autologous stem cell transplantation; n (%)	25 (76%)
Previous proteasome inhibitor; n (%)	
Bortezomib	33 (100%)
Carfilzomib	22 (67%)
Previous immunomodulatory drug; n (%)	
Lenalidomide	33 (100%)
Pomalidomide	23 (70%)
Previous anti-CD38 monoclonal antibody	
Daratumumab	33 (100%)
Isatuximab	0 (0%)

IQR interquartile range, *ISS* International Staging System, *MM* multiple myeloma

Efficacy

All patients received BM as monotherapy. At the time of data collection, seven patients were still on BM treatment. The median number of BM doses per patient was 3 (range, 1–16), and the median follow-up was 11.7 months (range, 0.8–14.9 months). The median time to BM treatment discontinuation was 2.0 months (95% CI 1.7–4.0).

Among the 26 patients (78.8%) who discontinued BM treatment, the reasons were progression disease (PD) in 18 patients (54.5%), AEs in five patients (15.1%), death in two patients (6.1%; due to multi-drug resistant *P. aeruginosa* infection [renal failure] and COVID-19 pneumonia) and patient's decision in one patient (3%).

The ORR was 42.2% (n = 14). One patient (3%) achieved stringent complete response (sCR), three patients (9%) achieved CR, two patients (6%) achieved very good PR (VGPR), and eight patients (24%) achieved PR. The CBR was 48% (two patients [6%] achieved MR).

The overall proportions of patients achieving a response in patient sub-cohorts are shown in Fig. 1.

At the time of data analysis, 21/33 patients (63.3%) were alive. The median PFS was 3 months (95% CI 0.9–5.1) in the overall population (Fig. 2A) and 11 months (HR 0.26; 95% CI 0.1–0.7) in those patients who achieved ≥ PR (Fig. 2B). No significant differences were found in PFS according to age, cytogenetic risk, and prior therapy lines (Fig. 3).

Median OS was 13.0 months (95% CI 3.6–24.7) in the overall population (Fig. 4A), with the better outcomes observed in the patients who achieved ≥ PR (Fig. 4B).

Safety

Overall, 67% (22/33) of the patients had at least one TEAE. Table 2 shows the TEAEs occurring during the BM treatment.

The incidence of hematological TEAEs was 21.2% (n = 7); with ≥ grade (G) 3 AEs reported in 18.2% (n = 6) of patients. Thrombocytopenia (21.2%) was the most common hematological TEAE.

The incidence of non-hematological TEAEs was 57.6%, with ten patients (30.3%) reporting ≥ G3 AEs, including ocular toxicity in eight patients. The most common non-hematological TEAE was keratopathy (51.5%), followed by patient-reported vision-related symptoms (45.5%) (Fig. 5). Regarding the ophthalmological exam findings, keratopathy and BCVA change to 20/50 or worse were resolved in 70.6% and 90% of the patients, respectively.

Dose reductions of BM were required in 30.3% of the patients and delayed in 36.4% due to TEAEs. Discontinuation of BM was required in 26 patients (78.8%) due to: progression (n = 18; 54.4%), toxicity (n = 5 [15.1%]: non-ocular toxicity [n = 2; 6.0%], only ocular toxicity, [n = 2; 6.0%], and non-ocular

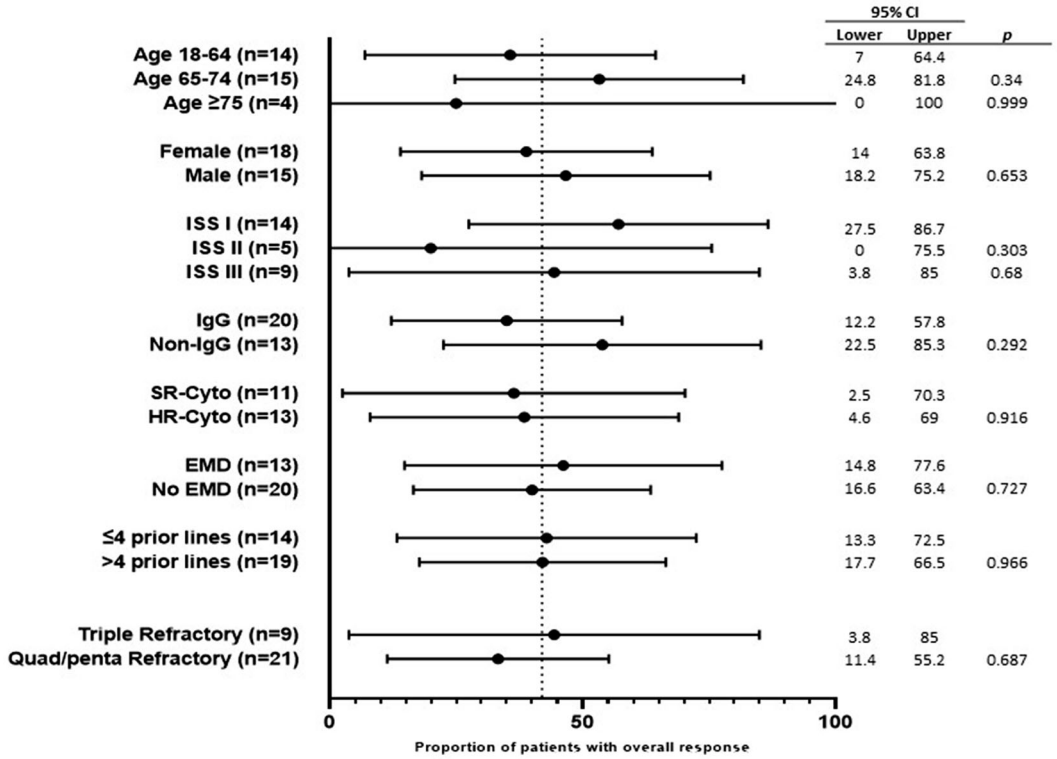

Fig. 1 Overall proportions of patients achieving a response according to different baseline characteristics subgroups

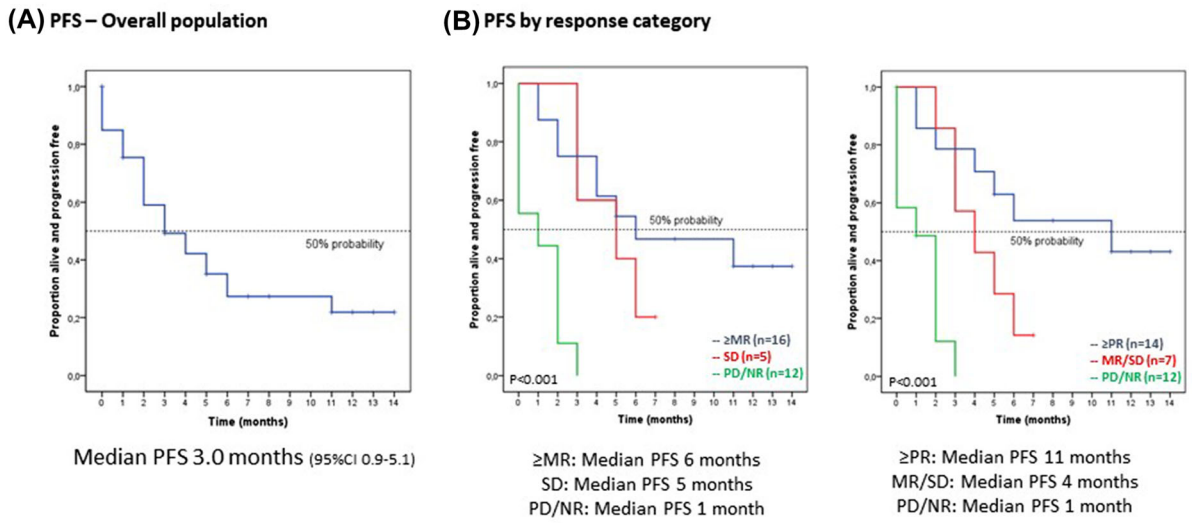

Fig. 2 Progression-free survival (PFS) outcomes with single agent BM in EAP. **A** PFS of the overall population. **B** PFS by response category

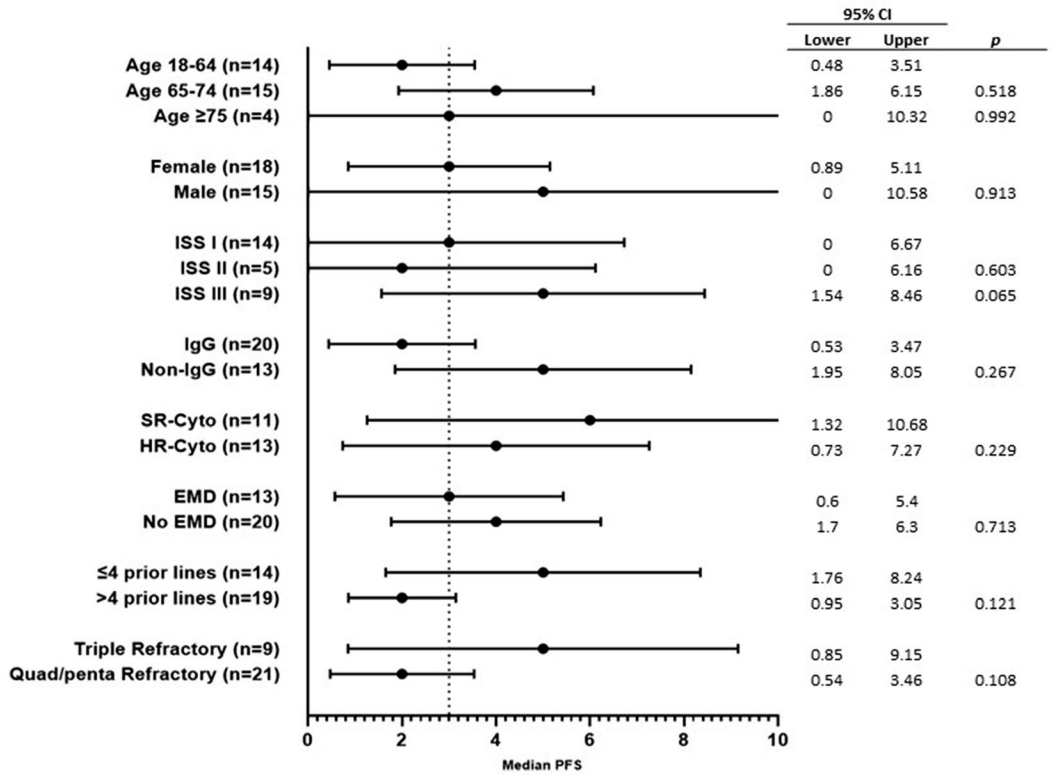

Fig. 3 Forest plot of median PFS of the patients included in the BM EAP according to different baseline characteristics subgroups

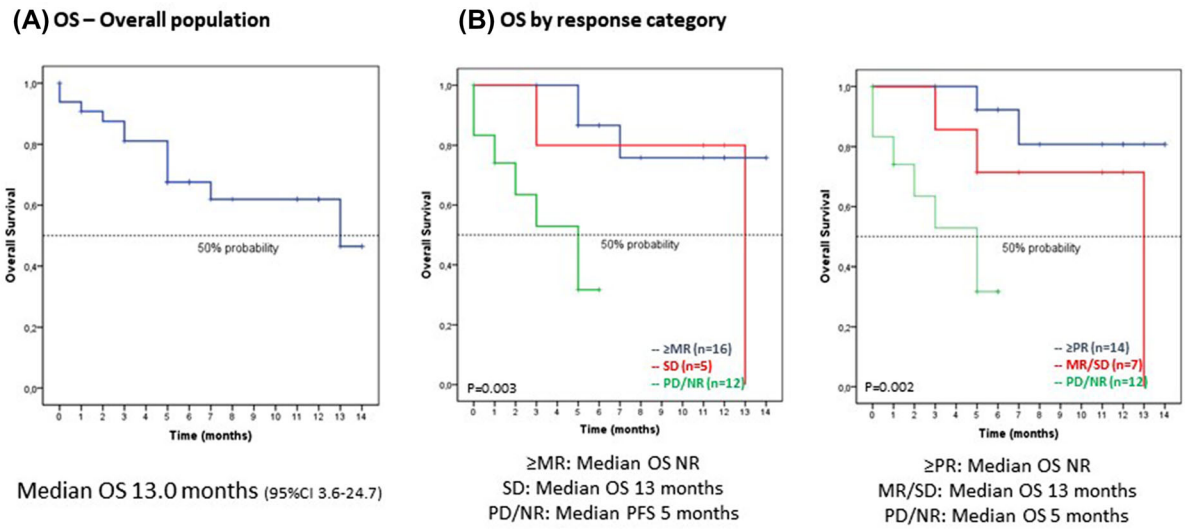

Fig. 4 Overall survival (OS) outcomes with single agent BM in EAP. **A** OS of the overall population. **B** OS by response category

Table 2 Adverse events occurring in patients during BM treatment

	EAP (n = 33)
Overall, n (%)	22 (67.0)
Hematological AEs, n (%)	
Overall	7 (21.2)
≥ Grade 3	6 (18.2)
Thrombocytopenia	7 (21.2)
Neutropenia	4 (12.1)
Anemia	2 (6.1)
Non-hematological AEs, n (%)	
Overall	19 (57.6)
≥ Grade 3	10 (30.3)
Vision-related symptoms reported by patients, n (%)	15 (45.5)
Blurred vision	10 (30.3)
Dry eye	8 (24.2)
Foreign body	3 (9.1)
Vision loss	2 (6.1)
Photophobia	1 (3.0)
Ophthalmological exam	
Keratopathy	
Overall	17 (51.5)
≥ Grade 3	7 (21.2)
Recovery	12 (70.6)
BCVA change to 20/50 or worse	
Overall	10 (30.3)
Recovery	9 (90.0)
Treatment, n (%)	
Artificial tears	28 (84.8)
Steroid eye drops	9 (27.3)
Autologous serum	1 (3.0)
Topical insulin	1 (3.0)
Infection[a]	3 (9.1)
AST/ALT increase	3 (9.1)
Fatigue	2 (6.1)
Tumor lysis[a]	2 (6.1)
Respiratory distress[a]	1 (3.0)
Acute myeloid leukemia[a]	1 (3.0)
Dose modifications due to AEs, n (%)	
Dose delay	12 (36.4)
Dose reduction	10 (30.3)
Discontinuation	5 (15.1)

AEs adverse events, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *BCVA* best-corrected visual acuity, *EAP* Expanded Access Program
[a]Not reported in the DREAMM-2 trial

toxicity + ocular toxicity [n = 1; 3.0%]), death (n = 2; 6.0%), and patient's decision (n = 1; 3.0%). Two of the patients requiring BM discontinuation, after 5 and 2 cycles, were on CR in the absence of BM treatment after 8 and 7 months, respectively. The patient that discontinued BM treatment due to ocular and non-ocular (cytopenia) toxicity, reintroduced BM after 1 year on CR.

Any prior eye condition may be associated with a higher risk of keratopathy after BM therapy (OR 15.8, 95% CI 1.7–148.1; p = 0.007).

DISCUSSION

BM represents a first-in-class antibody–drug conjugate (ADC) (anti-BCMA) with a multimodal mechanism of action against MM [26]. The FDA and EMA approved it following the phase II trial DREAMM-2, which included 97 patients including triple-class refractory MM [12, 14–16].

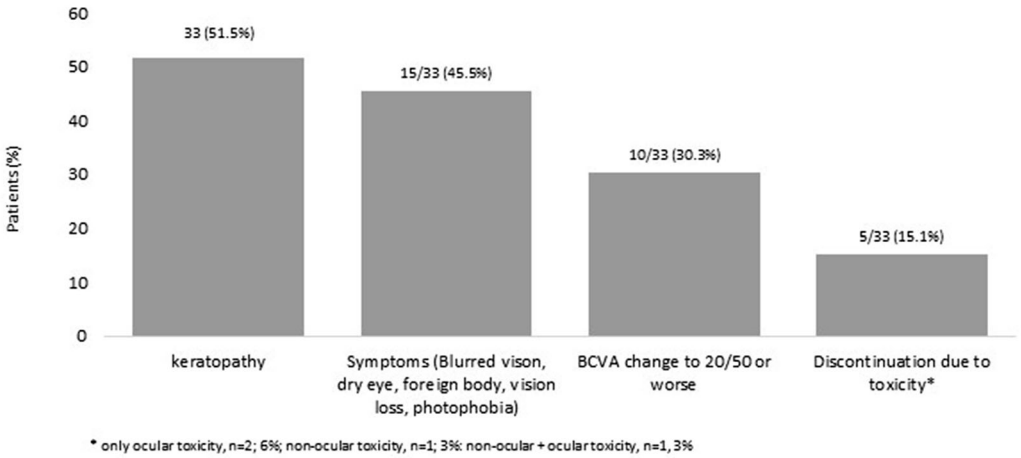

Fig. 5 Frequency of corneal and vision-related events in patients receiving BM (2.5 mg/kg)

We present the real-world experience of 33 patients with heavily pre-treated RRMM receiving BM monotherapy in the framework of the EAP from 14 hospitals in the Community of Madrid (Spain). It is an appreciable sample, considering that of the DREAMM-2 trial and the EAP time period of BM in Spain (Nov 2019 to Jun 2021).

The median age of our sample (70 years) was slightly higher than those of DREAMM-2 (65 years) [15]. When comparing our study with DREAMMS-2 regarding MM characteristics associated with poor prognosis, we found that our population had less patients with ISS III (28 vs. 43%) and high-risk cytogenetic (48 vs. 60%) but more patients with extramedullary disease (EMD) (39 vs. 23%). The prognosis of MM with EMD (incidence in RRMM patients, 3.4–14%) is considerably worse than for MM without EMD [27]. This characteristic may lead to the exclusion of patients from participation in trials, especially in advanced MM (heavily pre-treated patients), which may justify the scant evidence of treatment outcomes in patients with RRMM and EMD [27]. Reporting real-life data with this population could be very useful for increasing knowledge and improving patients' management, especially if data with new drugs are included.

A median of five lines of therapy was received prior to BM (two less than in the DREAMM-2), with a high percentage of triple- (88%), quad- (30%), and penta-refractory (33%) patients. This high rate of refractoriness with few lines of treatment reflects that the drug's mechanism of action is changed early in Spain. This finding, similar to that observed in other real-world experiences with BM [18, 22], can be justified by the availability of several generations of new anti-MM drugs in the front-line setting [28]. Earlier use of these new drugs promotes the achievement of relapsed/refractory status after primary refractoriness or early relapse after first-line treatment [28]. This clinical situation will likely increase, decreasing the number of patients with very late relapse after a long course of treatment (e.g., chemotherapy or autologous stem cell transplantation [ASCT] as first-line treatment) [28], such as those included in other real-world experiences with 7–8 prior lines before BM [12, 21].

Table 3 compares our cohort to DREAMM-2 (BM 2.5 mg/kg) in terms of patient characteristics and outcomes. Although both had a similar follow-up period and the same median cycles of BM 2.5 mg/kg [15], the efficacy and safety outcomes we observed were better. These results corroborate that BM is a new therapeutical option in the real world, with anti-MM activity and manageable safety profile for patients with triple-class exposure. In routine clinical practice, these patients are receiving a range of drug combinations that they have previously received, indicating limited options [29].

It has been previously reported (in solid tumors) that the survival outcomes achieved in

Table 3 Comparison of our cohort to the DREAMM-2 (2.5 mg/kg) cohort

	EAP (*n* = 33)	DREAMM-2 (*N* = 97)
Patients' characteristics		
Prior lines (median), *n*	5	7
≥ 4 lines	58	84
Age at BM administration, (mean) years	70	65
Extramedular disease; %	39	23
ISS III, *n* (%)	9 (28)	42 (43)
Age ≥ 75 years, *n* (%)	4 (12)	13 (13)
High risk cytogenetics, *n* (%)	16(48%)	41 (42)
	2(6)	16 (16)
Del17q	4 (12)	11 (11)
t(4;14)	0(0)	7 (7)
t(14;16)	10 (30)	25 (26)
1q21+		
BM treatment		
Cycles, median. *N* (range)	3 (1–16)	3 (1–17)
Time to discontinuation, median; m (95% CI)	2.0 (1.7–4.0)	2.1 (2.1–2.8)
Follow-up; median. m (range)	11.7 (0.8–14.9)	12.4 (0.9–17.1)
Dose delay due AEs; *n* (%)	12 (36)	51 (54)
	10 (30)	33 (35)
Dose reduction due to AEs; *n* (%)	5 (15)	9 (9)
Discontinuation due to AEs *n* (%)		
Efficacy outcomes		
Median PFS; m (95% CI)	3.0 (0.9–5.1)	2.8 (1.6–3.6)
Median PFS (pts ≥ PR)	11 m ((HR 0.26; 95% IC 0.1–0.7)	
Median OS (months)	13.0 (3.6–24.7)	13.7 (9.9–NR)
ORR (%)	42	32
sCR	3	2
CR	9	5
VGPR	6	11
PR	24	13
CBR	48	36

AEs adverse events, *BM* belantamab mafodotin, *CBR* clinical benefit rate, *CI* confidence interval, *CR* complete response, *EAP* Expanded Access Program, *HR* hazard ratio, *ISS* International Staging System, *m* months, *OS* overall survival, *PFS* progression free survival, *PR* partial response, *pts* patients, *sCR* stringent CR, *VGPR* very good PR

real-world patients are consistently equal or superior to those observed in the trial setting despite their unfavorable characteristics [30]. We also observed this with BM in MM, and in concordance with the published potential justification for this improvement [30], we think it can be promoted by the experience with the drug that fosters the optimization of its use.

Recently (2021) Vaxman et al. published another cohort of 36 patients receiving BM in the real world. However, their population was not comparable to ours because they had received more prior lines (median, 8), 19% had received an anti-BCMA CART previously, 8% had renal failure, and 17% received BM in combination (pomalidomide, cyclophosphamide, and thalidomide) [12]. Nevertheless, their efficacy results showed an ORR very similar to DREAMM-2, but with lower OS. The

difference with our results, with better ORR, could suggest a higher benefit of an earlier indication of BM (less pre-treated patients) without prior anti-BCMA therapy and used as monotherapy.

Surprisingly, our subgroup analysis of response rates according to baseline patients' characteristics did not show any differences between subgroups, even those with extramedullary disease and high-risk cytogenetics. In these subgroups, the ORR in DREAMM-2 was 5% and 29%, respectively [15], significantly reduced in the case of extramedullary disease compared to that of the overall population (32%). Our results must be interpreted with caution because the small sample in the subgroups analysis entails more uncertainty, as the wider confidence interval evidences. However, we did not observe major differences in the median PFS, with also strikingly good results in extramedullary disease and high-risk cytogenetics. Moreover, the best outcomes were in the patients with lower prior lines. In the analysis according to the response, the most relevant difference was observed in patients with stable disease, both in PFS and OS.

Regarding the safety profile, thrombocytopenia and corneal toxicity remain the most frequent AEs, with no new safety signals. All hematological AEs we detected (thrombocytopenia, neutropenia, and anemia) occurred less frequently than in the DREAMM-2 trial. Moreover, regarding the non-hematological AEs, we observed less keratopathy (52 vs. 72% in the DREAMM-2 trial). However, there were some AEs reported that were not common in the DREAMM-2, such as infection, tumor lysis, respiratory distress, and acute myeloid leukemia.

Regarding ocular toxicity, it must be considered that it is an unusual safety concern to handle in hematology. Due to this toxicity, BM is available through a restricted program under a risk evaluation and mitigation strategy. In the DREAMM-2 study, approximately 70% had ocular toxicity, manifesting as corneal epithelial changes, although only 6% permanently discontinued the drug due to keratopathy. In the real world, Shragai et al. [22] reported the same percentage of BM discontinuation due to ocular toxicity (6%) among 67 patients treated under the expanded access compassionate care program in nine Israeli centers. The real-world safety ocular data report with this drug has very important and practical implications.

In our experience, the events of keratopathy were 51.5%; 21.2% grade 3, and there was only dose reduction in 30.3% of patients, slightly lower than the reported in DREAMM-2 (35%); and lower dose delay in 36.4% of patients (54% in DREAMM-2). Perhaps the high percentage of dose discontinuations (18.2 vs. 9.0% in DREAMM-2) can justify this difference. In our study, only one patient (3%) permanently discontinued BM due to a corneal event, similar to the percentage reported in DREAM-2. Appropriate training in monitoring and managing this toxicity is mandatory with strict patient education and ophthalmological collaboration that could reduce the discontinuation in the real world. It is vital to maintain the treatment although modifications are required, especially as it has been observed that dose delays and reductions, and even prolonged interruption, have a minimal impact on patient responses with BM [15].

The mean time to treatment discontinuation was 2 months, very similar to that reported in DREAMM-2. This could reflect the early onset of toxicity of BM that may lead to discontinuation. However, it may also reflect that physicians discontinued BM if no early efficacy was observed. In the DREAMM-1 trial, the median time to first response was 1.2 months, and responses deepened over time [31]. Permanent discontinuation rate due to keratopathy is of major concern due to the potential impact in myeloma. This discontinuation rate is controversial in the real-world ranging from 6% [21, 22] to $> 10\%$ [32] in a short series of patients, and probably will decrease with better programs of prevention and ophthalmological surveillance as recommended by tools for improving and better managing ocular toxicity including material for professionals as described at Belantamab Eye care professional - Ocular Management Support Program (GSK) [23].

Our study has several limitations. Some are due to its retrospective nature and the lack of the date of the first response to the BM treatment affecting the calculation of the duration

of response. The small sample is another limitation, which affected the subgroup analysis. The number of cases and the time of follow-up of our registry are under expansion in our country to gain more experience with this new agent. Another limitation is that none of the patients included had renal failure or any anti-BCMA prior therapy, which could allow the assessment of the real impact and help practitioners identify patients potentially eligible for BM treatment. Finally, more evidence is needed on the sequential use of anti-BCMA agents because patients previously exposed were excluded in trials and the few published cases report mixed outcomes [12].

CONCLUSIONS

Our real-world experience of BM in heavily pre-treated RRMM appears to be consistent with those observed in the pivotal DREAMM-2 study (efficacy and safety). This means that BM is an actual new option for heavily pre-treated triple-class RRMM patients with limited therapeutical options and a poor prognosis. This new drug is being evaluated combined with other drugs and in an early stage of disease in the DREAMM clinical trial programs.

Adequate measures to successfully prevent and mitigate ocular toxicity are necessary and should be adopted to prevent major ocular toxicity to avoid permanent discontinuation of BM treatment, compromising clinical results. Additional patients and updated follow-up will be required to assess the real impact and get more experience.

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Compliance with Ethics Guidelines. All procedures in this study met the bioethical standards outlined in the Helsinki Declaration [24]. This study was approved by the local ethics committee (Hospital Universitario Ramón y Cajal; committee's reference number: 337-21) and all patients provided written informed consent.

Data Availability. The original data and protocols are available to all the investigators

without unreasonable restrictions with access to the data registry.

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