Real-world study of the efficacy and safety of belantamab mafodotin (GSK2857916) in relapsed or refractory multiple myeloma based on data from the nominative ATU in France: the IFM 2020-04 study

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Received: October 14, 2022.
Accepted: April 11, 2023.
Early view: April 20, 2023.

https://doi.org/10.3324/haematol.2022.281772

Abstract

Belantamab mafodotin (BM) is an anti-BCMA antibody-drug conjugate (GSK2857916) that represents an alternative option in multiple myeloma. We sought to assess the efficacy and safety of BM in a real-world setting in patients who benefited from an early access program. We conducted an observational, retrospective, multicenter study. Eligibility criteria were treatment of relapsed or refractory multiple myeloma (RRMM) in monotherapy in adult patients who have received at least three lines of therapy previously, including at least one immunomodulatory agent (IMiD), a proteasome inhibitor (PI) and an anti-CD38 monoclonal antibody, and whose disease progressed during the last treatment period. The primary endpoint of the study is to assess the overall survival (OS). Between November 2019 and December 2020, 106 patients were treated with BM; 97 were eligible for the efficacy evaluation and 104 for safety. The median age was 66 (range, 37–82) years. High-risk cytogenetics were identified in 40.9% of patients. Fifty-five (56.7%) patients were triple-class refractory and 11 (11.3%) were penta-class refractory. The median number of prior lines of treatment was five (range, 3–12). The median number of BM cycles administered was three (range, 1–22). The overall response rate at best response was 38.1% (37/97). The median OS was 9.3 months (95% confidence interval [CI]: 5.9-15.3), and median progression-free survival was 3.5 months (95% CI: 1.9-4.7). The median duration of response was 9 months (range, 4.65-10.4). Treatment was delayed for 55 (52.9%) patients including 36.5% for treatment-related toxicity. Ophthalmic adverse events, mainly grade ≤2, were the most common toxicity (48%). The occurrence of keratopathy was 37.5%. Overall, our data are concordant with the results from DREAMM-2 in terms of efficacy and safety on a non-biased population.

Introduction

Effective and safe novel therapies are needed for the treatment of patients with relapsed or refractory multiple myeloma (RRMM). The course of the disease consists in multiple relapses, as MM is still not curable. The treatment of RRMM is particularly challenging after the use of the three principal MM drug classes: immunomodulatory drugs (IMiD), proteasome inhibitors (PI) and anti-CD38 monoclonal antibodies (mAb). Even though the range of options has widened in recent years, especially with the emergence of immunotherapy, RRMM still has a poor prognosis, and, therefore, new drugs with innovative mechanisms are necessary.

Belantamab mafodotin (GSK2857916) (BM) is a first-in-class IgG1 humanized anti-BCMA (B-cell maturation antigen) mAb conjugated to a cytotoxic agent, monomethyl auristatin F (MMAF), via a protease-resistant maleimidocaproyl linker. BM binds to BCMA on the surface of plasma cells (PC) and delivers MMAF directly into PC, thereby promoting apoptosis. BM has recently proven effective for heavily pretreated RRMM in the first-in-human phase I DREAMM-1 study, which led to a phase II study called DREAMM-2.[1–4] This study was an open-label two-arm study for RRMM patients whose disease had progressed after ≥3 prior lines of treatment and who were refractory to IMiD, PI and anti-CD38 mAb. In DREAMM-2, 196 patients received single-agent intravenous BM at either 2.5 mg/kg (97 patients) or 3.4 mg/kg (99 patients) for a 3-week cycle until disease progression or unacceptable toxicity. BM demonstrated a promising anti-tumor activity with an overall response rate (ORR) of 31% (97.5%; 95% confidence interval [CI]: 20.8–42.6) in the 2.5 mg/kg cohort and 34% (97.5%; 95% CI: 23.9–46.0) in the 3.4 mg/kg cohort. After a median follow-up of 6 months, the median progression-free survival (PFS) was 2.9 months (95% CI: 2.1–3.7) and 4.9 months (range, 2.3–6.2) in the two groups, respectively. Regarding tolerance, the main toxicity was corneal toxicity, with one quarter of patients exhibiting grade 3 or 4 disorders. After considering the benefit-risk balance, the 2.5 mg/kg dose was recommended for clinical use.

Based on these results, temporary utilization of BM was approved in France by the French National Agency for the Safety of Medicine and Health Products (ANSM) under an ATU (“autorisation temporaire d’utilisation”) format, thus providing early access to BM for RRMM patients. We designed a retrospective study using data from this temporary utilization, so-called “nominative ATU”, to further explore the efficacy and safety of BM in RRMM in a real-life context.

Methods

Study design

This study (IFM 2020-04) was an observational, retrospective, multicenter study that enrolled patients treated with BM as part of the ATU program in France from when the authorization began on September 17, 2019. Eligible patients had received at least one cycle of BM (GSK2857916) monotherapy whose indication as part of the ATU was the treatment of RRMM in adult patients who had received at least three lines of therapy previously, including at least one IMiD, a PI and an anti-CD38 mAb, and whose disease progressed during the last treatment period. The trial was sponsored by the French group IFM (“Intergroupe Francophone du Myélome”) and supported by GSK. This study was

conducted in full compliance with the principles of the Declaration of Helsinki with non-opposition of the patients and complies with the regulations in force in France for this type of clinical investigation on patients.

Outcomes

The primary outcome was to evaluate the efficacy and safety of BM (GSK2857916) in a real-world context as part of the nominative ATU for patients with RRMM who had received at least three previous lines of therapy. The safety population includes all patients who received at least one cycle of BM. The efficacy population includes all patients of the safety population with the evaluation of the main criterion (non-missing status: alive or dead at the last news) and satisfying inclusion criteria. The primary goal of the study was to assess the overall survival (OS) of patients following BM treatment. The secondary goals were to analyze real-world efficacy of BM based on the response rate (overall response rate [ORR], according to IMWG definition[5]), the time to response and duration of response (DOR), to proceed to a survival analysis with the progression-free survival (PFS) and event-free survival (EFS, calculated as the time from the first administration treatment to the date of disease progression event or permanent treatment discontinuation or death, whichever occurred earlier), to determine the time-to-next treatment (TTNT) defined as the time from first administration of BM to the date of the new line of treatment or death, time to progression (TTP), time to discontinuation and to focus on specific subset of patients such as high-risk (HR) or frail patients, and toxicity (according to NCI-CTC V5.0 criteria) taking into account the results of the DREAMM-2 phase II clinical trial. HR patients were displaying adverse cytogenetics features such as del(17p), t(4;14), del(1p32) or 1q gain.

Statistical analysis

Quantitative variables will be described in terms of extreme values, quartiles, median, or mean and standard deviation for data with a normal distribution (95% CI). Qualitative variables will be described in terms of headcount and proportions (with a 95% CI, binomial law). Survival data (PFS and OS) are estimated using the Kaplan-Meier method. Median survival times with a 95% CI and median follow-up are estimated using the inverted Kaplan-Meier method. The duration of response is described in responding subjects using descriptive statistics (median, range). The database is reported in compliance with the General Data Protection Regulation (GDPR).

Results

Baseline characteristics

The IFM 2020-04 study enrolled 106 patients overall. Patients were treated between November 2019 and December 2020. The safety and efficacy populations were composed of 104 and 97 patients, respectively (Figure 1). Baseline characteristics of the patients are presented in Table 1. The median age at diagnosis was 66 years (range, 7–82), and 49 patients (50.5%) were male. The median time

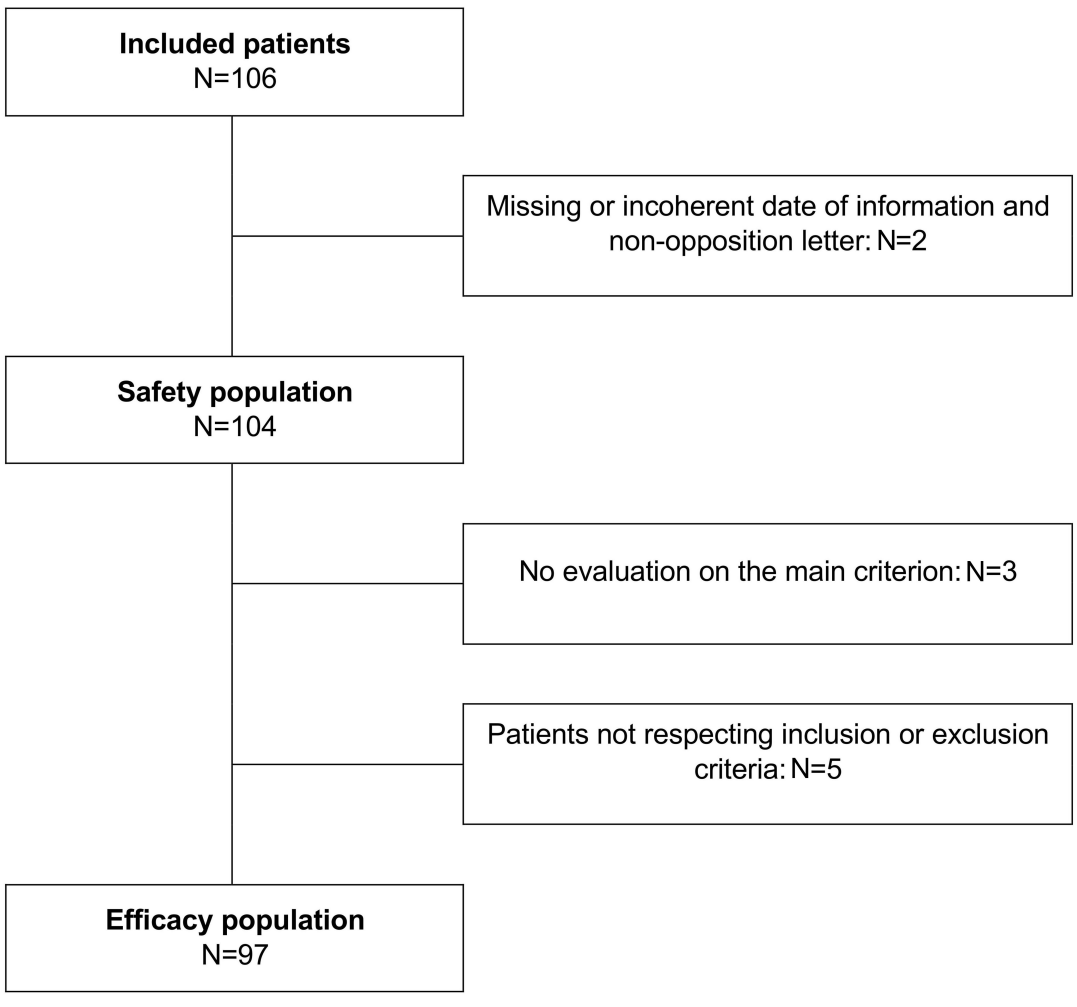

Figure 1. Flow chart. Identification of patient populations

Table 1. Baseline characteristics.

Variable	Cohort (N=97)
Age in years, median (range)	66 (37-82)
Sex, N (%) Male Female	 49 (50.5) 48 (49.5)
ISS, N (%) 1 2 3	 25/69 (36.2) 27/69 (39.1) 17/69 (24.6)
High-risk cytogenetics at diagnosis, N (%)	27/66 (40.9)
Extramedullary disease, N (%)	13/93 (14.0)
Median prior lines of therapies, N (range)	5 (3-12)
Triple-class exposed patients, N (%)	97 (100)
Triple-class refractory patients, N (%)	55 (55.6)
Penta-refractory patients, N (%)	11 (11.3)
Refractory status, N (%) Bortezomib Ixazomib Carfilzomib Thalidomide Lenalidomide Pomalidomide Daratumumab Isatuximab	 26 (26.8) 24 (24.7) 53 (54.6) 9 (9.3) 43 (44.3) 60 61.9) 60 (61.9) 9 (9.3)
Prior autologous stem cell transplant, N (%)	70 (72.2)
Time from diagnosis to treatment in years, median (range)	6.37 (1.19-19.61)
ECOG at treatment start, N (%) 0-1 >1	 57/82 (69.5) 25/82 (30.5)
Charateristics before BM initiation Median M spike, g/L Median hemoglobin, g/dL Median white blood cell count, x10^9/L Median platelet count x10^9/L Median creatinine, µmol/L Median GFR, mL/min/1.73m^2	 14.8 10.15 4.45 149 83.5 70

ISS: international staging system; ECOG: eastern cooperative oncology group; BM: belantamab mafodotin; GFR: glomerular filtration rate.

from MM diagnosis was 6.37 years (range, 1.19–19.61), 57 of 82 (69.5%) patients were fit as defined by Eastern Cooperative Oncology Group (ECOG) performance score ≤1, and three of 82 (3.9%) were frail as defined by ECOG ≥2 and ≥75 years old at treatment initiation. Concerning MM disease, 27 of 66 (40.9%) patients had HR cytogenetics and 13 of 93 (14%) had an extra-medullary disease (EMD). Patients had received a median of five (range, 3–12) prior lines of MM treatment. Regarding the treatments before BM, 55 (56.7%) patients were triple-class refractory (IMiD, PI, anti-CD38 mAb) and 11 (11.3%) were refractory to bortezomib, lenalidomide, carfilzomib, pomalidomide, and daratumumab (pentarefractory). Besides, 70 (72.2%) patients underwent prior autologous stem cell transplant (ASCT). Based on the safety population (data from 100/104 patients), the treatment criteria were a biological relapse for 44 patients (44.0%), a clinical relapse for 29 (29.0%), and both a biological relapse and a clinical relapse for 27 (27.0%).

Treatment and response

The median number of BM cycles administered was three (range, 1–22). The ORR at best response was 38.1% (37/97). The best response rates are summarized in Table 2. At 12±3 weeks, ORR was 35.6 % (26/73), including five patients (6.8%) with a complete response (CR), seven (9.6%) with a very good partial response (VGPR), and 14 (19.2%) with a partial response (PR), and eight (11.0%) patients had a stable disease (SD). The median time to achieve the best response was 2.05 months (range, 0–14.03). The median duration of response (DOR) was 9 months (range, 4.65-10.4). The DOR according to the best response is shown in Figure 2. The median TTNT was 4.25 months (95% CI: 3.17-6.6). The estimated incidence of treatment response was 21.8% at 3 months, 56.2% at 6 months, and 57.8% at 1 year.

Survival analysis

The median OS was 9.3 months (95% CI: 5.9-15.3) (Figure 3A), and median PFS was 3.5 months (95% CI: 1.9-4.7) (Figure 3B). The median EFS was 2.4 months (range, 1.4–3.5). Similarly, median OS for both high-risk (n=27/66) and standard-risk (n=39/66) patients was 9.2 months. The median OS was 14 months in patients with EMD (n=13/93), and 9.1 months in patients without EMD (n=80/93) (hazard ratio [HR]=1.04, 95% CI: 0.49-2.20). The median OS was 8.5 months in patients previously treated by less than 6 lines (n=51) and 10.2 months in patients previously treated by ≥6 lines (n=46) (HR=0.80, 95% CI: 0.47-1.35). The median OS was 16.8 months in fit patients and 6 months in unfit patients (HR=2.16, 95% CI: 1.18-3.95); two-tailed *P*=0.0103) (*Online Supplementary Table S1*). Kaplan-Meier curves of OS and PFS according to the best responses are presented in Figure 4. The median PFS was 2.7 months (95% CI: 1.6-4.3) in patients with triple-class refractory MM and 3.3 months (95% CI: 1.4-26.0) in patients without triple-class refractory MM (two-tailed *P*=0.7686). The estimated incidence of disease progression was 30.4% at 3 months, 47.8% at 6

Table 2. Best response (N=97).

Response rate, N (%)	Cohort (N=97)
Complete response	8 (8.2)
Very good partial response	11 (11.3)
Partial response	18 (18.6)
Stable disease	29 (29.9)
Not evaluable	31 (32.0)
Overall response rate	37 (38.1)

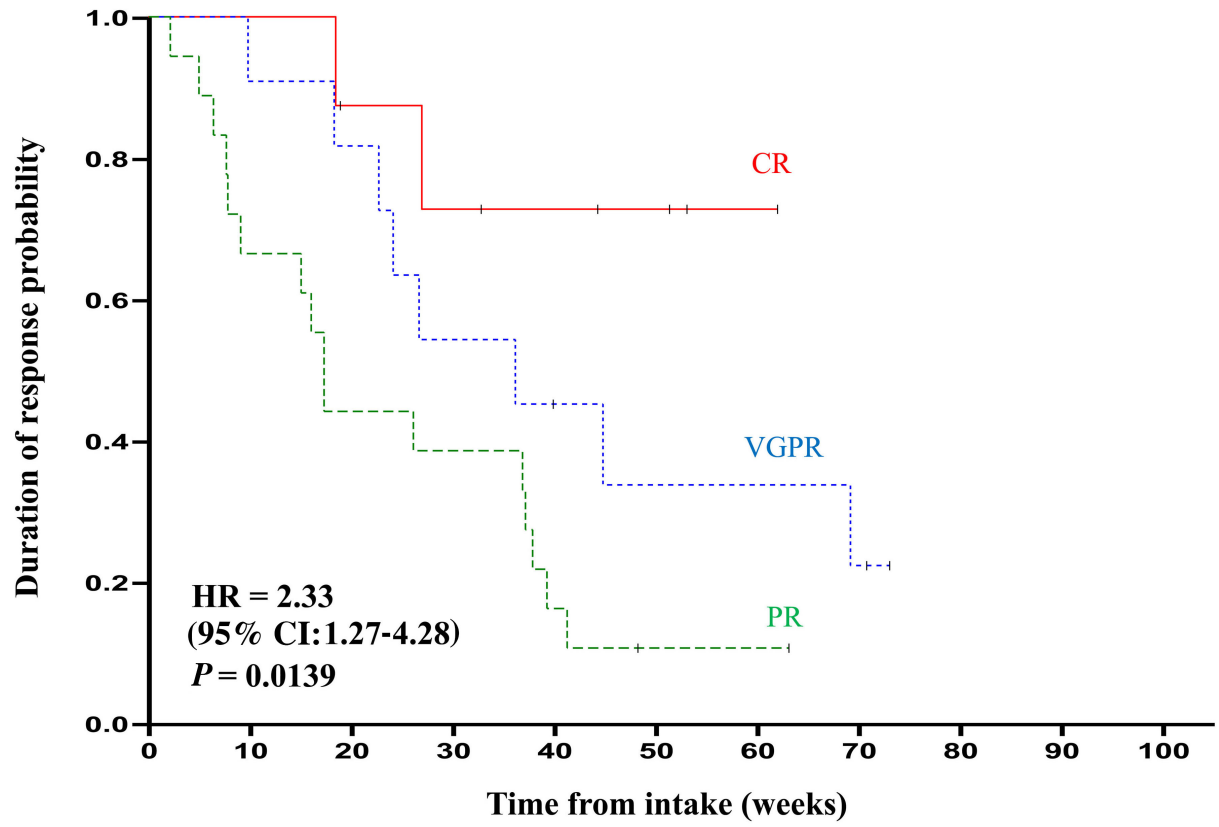

Figure 2. Duration of response according to the best responses. CR: complete response; VGPR: very good partial response; PR: partial response; HR: hazard ratio; CI: confidence interval.

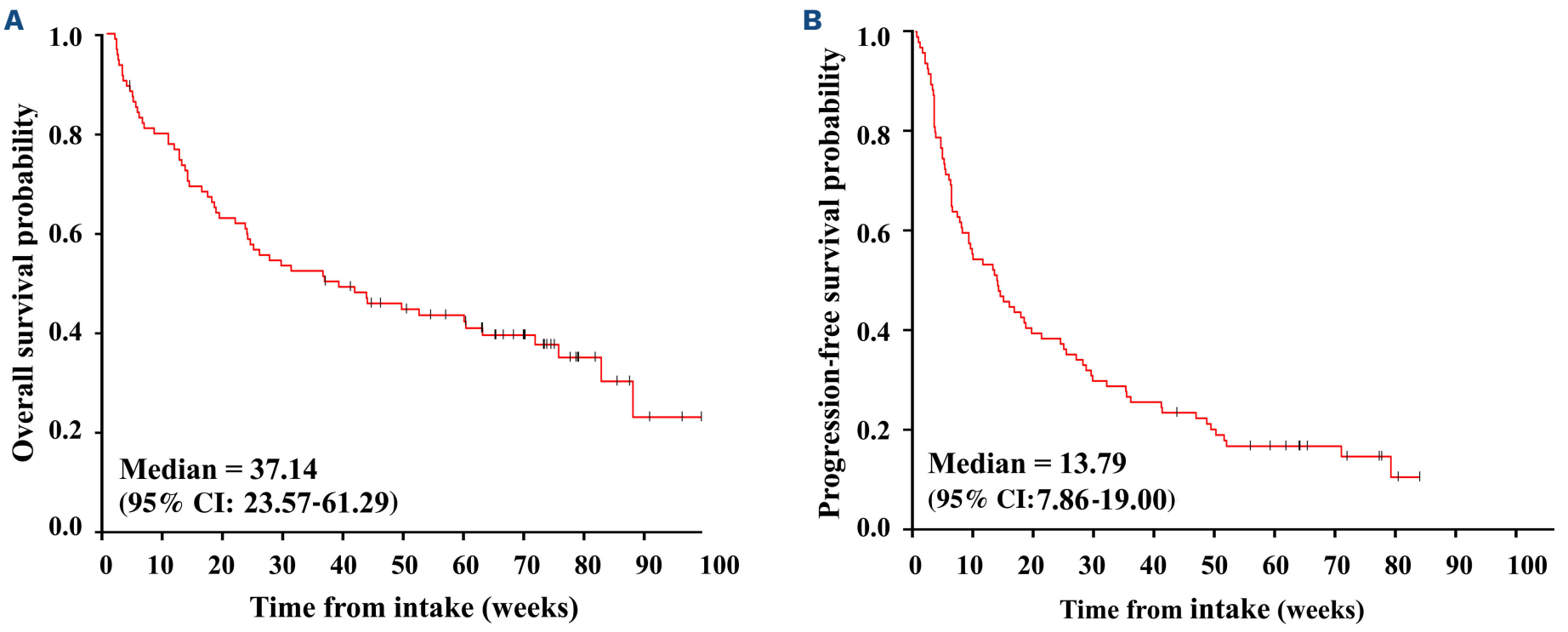

Figure 3. Kaplan-Meier survival curves of overall survival and progression-free survival in the efficacy population (N=97). (A) Overall survival and (B) progression-free survival; CI: confidence interval.

months and 67.6% at 1 year. At data cut-off (March 10th, 2022), 69 (67%) patients in the cohort had passed away; for 47 (68%) this was due to disease progression, for 12 (17%) it was due to infection and for two (3.0%) it was due to both progression and infection.

Safety

BM was administered every 21 days intravenously in monotherapy. The treatment was stopped for 55 (52.9%) patients, comprising 38 (36.5%) for treatment-related toxicity, and 14 of them experienced a treatment interruption more than once. The median duration of BM treatment was 1.4 months and patients received a median of three treatment cycles (range, 1-22). The median time for the first interruption since the start of BM was 1.6 months (range, 0–13.3). For 42 patients, the treatment was restarted after a median time of interruption of 29 days (range, 1–300). Dose reductions were reported for 23 (22.1%) patients, mostly from 2.5 mg/kg to 1.9 mg/kg, as the first dose reduction. The minimal dose used was 1.4 mg/kg for one patient. Ophthalmic toxicity was observed for 49 of 102 (48%) patients (Table 3). Of the patients who

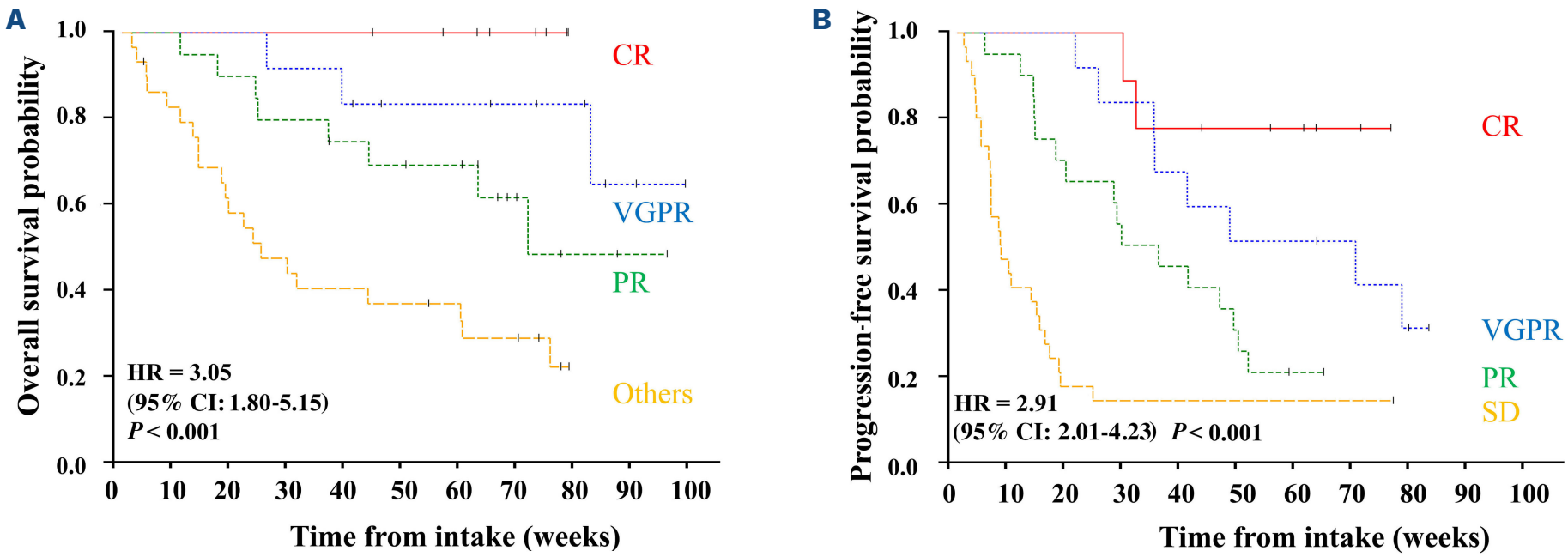

Figure 4. Survival according to best responses (N=66). (A) Overall survival according to best response. (B) Progression-free survival according to best response. CR: complete response; VGPR: very good partial response; PR: partial response; SD: stable disease; HR: hazard ratio; CI: confidence interval.

experienced ophthalmic toxicity, the keratopathy percentage was 81,3% (n=39/48) and the percentage of reduced visual acuity was 4.8%. Ophthalmic toxicity was mainly grade ≤2 (55%) and no grade 4 was observed. Ocular events resulted in delayed treatment administration or in a dose reduction in 30% of concerned patients. Premedication before BM was used for 91.3% of patients and 64 (61.5%) patients received premedication with eye drops to limit ocular toxicity before the infusion of BM. Besides, 16 (15.4%) patients developed grade 3 or 4 hematologic toxicity. Hematologic toxicity was principally marked by thrombocytopenia (43.8%). Grade 3 or 4 non-hematologic toxicity was reported in nine (8.7%) patients. Ten (9.6%) patients had infusion-related reactions (IRR) of any grade (80% of grade ≤2), mostly at the first two cycles. One patient had a grade 3 bronchospasm at cycle 6. Of note, nearly 40% of patients received paracetamol or antihistaminic agent before BM was administered.

Table 3. Adverse event in 104 patients (safety population).

Adverse events	Safety cohort (N=104)
Ocular toxicity, N (%)	49/104 (48)
Grade 1-2	26/49 (53.1)
Grade 3	20/49 (40.8)
Overall keratopathy, N (%)	39/104 (37.5)
Overall BCVA changes, N (%)	5/104 (4.8)
Other AE, N (%)	4/104 (8.3)
Grade 3-4 hematologic toxicity, N (%)	16/104 (15.4)
Anemia	2/16 (12.5)
Leuco-neutropenia	3/16 (18.8)
Pancytopenia	4/16 (25)
Thrombopenia	7/16 (43.8)
Grade 3-4 non-hematologic toxicity, N (%)	9/104 (8.7)
Infusion reaction, N (%)	10/104 (9.6)

BVCA: best visual corrected acuity; AE: adverse events.

Discussion

The clinical course of MM is characterized by multiple relapses and finally patients lack treatment options and therefore their survival is impacted.[6] The BCMA was recently found as a promising target for the development of naïve and armed immunotherapies, which extended the options in the relapse setting. Currently, several anti-BCMA therapies are emerging and being investigated, including bispecific antibodies (bsAb), chimeric antigen receptor T (CAR T) cells, and antibody-drug conjugates (ADC). Belantamab mafodotin proved effective in the phase II DREAMM-2 trial. Based on the data from this trial, a temporary utilization program (ATU program) in France was authorized for patients with RRMM to benefit to an early access to the molecule.

Our real-life cohort included 106 patients, with 97 in the efficacy population which is the same number as in the DREAMM-2 2.5 mg/kg cohort. We present the highest percentage of responding patients compared to the literature (ORR 38.1%). Survival rates are also notable with a median OS of 9 months and median PFS of 3.5, which is in line with previous studies on BM. As a comparison, the last line of treatment before BM was administered for five cycles in median and the best response rate were: seven CR (7.8%); 17 VGPR (18.9%); 27 PR (30.0%), and 39 SD (43.3%), ORR at 56.7%. In the best response related to the next treatment following BM (n=36) 23 patients (63.9%) had stable disease, seven PR (19.4%), three VGPR (8.3%)

and three CR (8.4%), ORR was 36.1%.

Moreover, the toxicity profile of BM was similar to the previous studies that investigated it, as it essentially consisted of ophthalmological and hematological adverse events (AE). The keratopathy rate was 37% and mainly low grade. Ocular toxicity was reversible, as the median duration of delay was 29 days, which means in "real-life" the management of ophthalmological AE seems manageable. We did not report any unexpected AE compared to other BM studies.[3]

The better response rates might be explained by the lower number of previous line (median of 5 prior lines) in comparison to the DREAMM-2 (median of 7 prior lines) cohort and another real world study from the mayo clinic (median of 8 prior lines).[8] Table 4 compares the different variables from our study, DREAMM-2 and the Mayo Clinic study. One major difference is that in our study, not all patients (55%) were triple-class refractory (refractory to an IMiD, a PI, and an anti-CD38). Patients had to be exposed to all three classes to benefit from the ATU program. Even though patients from our study had better responses, the median OS is longer in the extended 13-month follow-up of DREAMM-2. Interestingly, in subgroup analysis, no significant difference was observed in terms of OS, PFS and TTNT for patients with extramedullary disease (*Online Supplementary Table S1*; *Online Supplementary Figure S1*) as well as with ORR (*Online Supplementary Figure S2*). In addition, the keratopathy rate was nearly similar to the real-life one reported by the Mayo clinic and were both lower than in DREAMM-2. We can hypothesize either that AE were less reported than in a clinical trial or that the management of ocular toxicity has improved since DREAMM-2.

Anti-BCMA treatments are increasingly being used for patients with RRMM, as most of patients will eventually be exposed and refractory to anti-CD38 mAb.[6] A novel target was, therefore, needed for advanced patients so that they can still benefit from immunotherapy.[9] Currently, innovative immunotherapies targeting BCMA include CAR T cells, bsAb and ADC.[10–14] Even though CAR T and bsAb might seem more appealing because of their efficacy,[15] BM still represent an alternative anti-BCMA treatment. Non-immunologic agents, although still necessary, are usually associated with toxicities such as selinexor[16,17] or melflufen,[18] whose development has been put on hold, and therefore immune-based treatment such as BM offer innovative strategies. To contextualize median OS of 9.3 months, we found a median OS of about 3-4 months for

Table 4. Comparison between our cohort (IFM 2020-04) and the DREAMM-2 and Mayo Clinic studies.

Variable	IFM 2020-04 cohort N=97	DREAMM-2 cohort (2.5 mg/kg) N=97	Mayo Clinic cohort N=36
Age in years, median (range)	66 (37-82)	65 (60-70)	61 (37-83)
Sex, N (%) Male/Female	49 (50.5)/48 (49.5)	46 (47)/51 (53)	23 (64)/13 (36)
Median creatinine (μmol/L)	83.5	-	96.8
High-risk cytogenetics at diagnosis, N (%)	27 (40.9)	41 (42)	14 (41)
Extramedullary disease, N (%)	13 (14.0)	22 (23)	5 (14)
Median prior lines of therapies, N (range)	5 (3-12)	7 (3-21)	8 (7-11)
Prior ASCT, N (%)	70 (72)	73 (75)	27 (75)
Triple-class refractory patients, N (%)	55 (55.6)	97 (100)	36 (100)
Median OS in months	9.5	13.8	6.5
Median PFS in months	3.2	2.8	2
ORR, %	38	32	33
CR, %	8	7	6
VGPR, %	11	11	8
PR, %	18	13	19
Keratopathy, %	37	67	43

ASCT: autologous stem cell transplant; OS: overall survival; PFS: progression-free survival; ORR: overall response rate; CR: complete response; VGPR: very good partial response; PR: partial response.

MAMMOTH-like MM patients in a French national healthcare database OS study.[6,19] BM represents a promising alternative option for these patients with its unique mechanism of action for the delivery of the cytotoxic agent directly into MM cells after binding BCMA.

Real-world patients are not those selected according to the strict inclusion and exclusion criteria for a clinical trial. Most fragile patients with multiple comorbidities and particularly aggressive diseases are generally not included in the trials. The results of the trials, therefore, have strong internal validity, but cannot be extrapolated for the wider and clinically more heterogeneous population. Real-life data, though not collected in an international setting, are now considered a major issue to confirm or refute the outcome of patients actually exposed to the treatment.

We note several limitations of this study. It is limited by its retrospective nature, and, therefore, some data are lacking for several patients. Nevertheless, we present the largest real-life cohort of patients, which is comparable to the DREAMM-2 study. No exclusion criteria were defined, and, therefore, this study is composed of patients who might have presented with renal failure and with an impaired performance status.

Overall, the results of our retrospective real-life study are concordant with the previously reported results of the phase II clinical trial DREAMM-2 in terms of response, survival, and toxicities. Although the ophthalmological issues are a concern,[20–22] BM remains an alternative option for previously highly treated patients that can thus benefit from an anti-BCMA therapy in the late course of disease. We expect that the management of AE will improve with increased use of the drug.[23]

Disclosures

AP is part of the advisory board of AbbVie, Amgen, BMS/Celgene, GSK, Janssen, Pfizer, Sanofi and Takeda. LG is part of the advisory board of Abbvie, Pfizer, BMS, GSK and Immunocore. LK is part of the advisory board of AbbVie, Janssen, Novartis and Takeda; received personal fees from AbbVie, AstraZeneca, BeiGene, iQone, Novartis, Seagen and Takeda. PM is part of the advisory board and received honoraria from Janssen, Celgene, Amgen, Takeda, Sanofi and Abbvie. RLC is part of the advisory board of Takeda and Abbvie; acts as a consultant for Takeda, Abbvie and Gilead. RP is part of the advisory board of GSK. XL received honoraria from Janssen, Bms, Novartis, Amgen, Sanofi, Takeda, Pfizer, GSK and Roche.

Contributions

AT, AB, XL, BA and HAL developed the concept and designed the study. AT, AB, LT, CB, CD, MOP, OA, PA, PA, RB, SC, DC, MLC, OD, PF, LF, LG, AH, CH, LK, KL, RLC, PL, MM, SM, JPM, SM, PM, VM, JM, FOP, AP, GMP, PR, AS, AMS, PT, CT, VV, MV, LV, ZVDW, CZ, XL, BA and HAL collected and assembled the data. AT, AB, LT and HAL analyzed and interpreted the data. AT, AB, LT and HAL wrote the article. All authors read and approved the final version of this manuscript.

Acknowledgments

The authors wish to thank the patients and families, the centers that participated to the study, the IFM teams and the statistical team (Statitec - MultiHealth Group).

Funding

The trial was sponsored by the French group IFM and supported by GSK.

Data-sharing statement

The original contributions presented in the study are included in the article and its Online Supplementary Appendix. Further inquiries can be directed to the corresponding author.

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