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SHORT REPORT

B-cell maturation antigen-based therapies post-talquetamab in relapsed or refractory multiple myeloma

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Abstract

Talquetamab recently received approval for relapsed refractory multiple myeloma. However, there is currently no available data on how patients perform with BCMA based agents after progression on talquetamab. Herein, we present the outcome of 10 patients who received BCMA based therapies following talquetamab. The median follow-up was 9.5 months (range: 6–24 months). The median progression free survival was 5.5 months (range: 1–10 months). Patients had varying grades of cytokine release syndrome and Immune effector cell-associated neurotoxicity syndrome. Our results suggest that treatment with talquetamab followed by BCMA based therapies is feasible and can be considered as clinically indicated.

KEYWORDS
BCMA, bispecific antibodies, CAR-T therapy, GPRC5D, multiple myeloma, sequencing, talquetamab

1 | INTRODUCTION

Multiple myeloma poses a significant challenge due to frequent relapses despite achieving initial remission. Patients often develop resistance to standard treatments like proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and anti-CD38 monoclonal antibodies, resulting in a median overall survival of only 9–12 months at the time of relapse [1, 2]. B-cell maturation antigen (BCMA) has emerged as a promising target for relapsed or refractory multiple myeloma (RRMM). Current therapeutic approaches for BCMA targeting include antibody-drug conjugates (ADCs), bispecific antibodies (BsAbs), and anti-BCMA chimeric antigen receptor (CAR)-T cell therapies [3]. However, the optimal sequencing of these treatments remains uncertain. Talquetamab, a bispecific antibody targeting CD3 and G protein-coupled receptor, family C, group 5, member D (GPRC5D) receptors, exhibited an overall response rate (ORR) of 64%–70% in heavily pretreated RRMM patients in the MonumenTAL-1 study [4, 5]. BCMA-based therapies were approved prior to the recent approval of talquetamab, thus how patients perform with BCMA-targeted therapies after failure of talquetamab is unknown. In an effort to bridge this knowledge gap, we present a case series analyzing the effectiveness of BCMA-based therapy in patients previously treated with talquetamab.

2 | METHODS

This retrospective study involved patients diagnosed with RRMM who underwent BCMA-based therapies subsequent to talquetamab progression at the University of Arkansas for Medical Sciences. Eligible patients had previously received treatment with a PI, an IMiD, and an anti-CD38 monoclonal antibody. Medical records were accessed to

gather data encompassing demographic information, baseline disease characteristics, prior therapies, laboratory parameters, treatment responses, and adverse events (AEs) after gaining Institutional Review Board approval. Cytokine release syndrome (CRS) and Immune effector cell-associated neurotoxicity syndrome (ICANS) AEs were graded according to the criteria of the American Society for Transplantation and Cellular Therapy [6]. Treatment response was evaluated using the International Myeloma Working Group (IMWG) criteria. Progression-free survival (PFS) was calculated from the date of the initiation of the BCMA-based therapy to the date of disease progression, death, or last known follow-up. ORR was defined as partial response (PR) or better according to IMWG response criteria. R statistical software version 4.0.5 (R Project for Statistical Computing) was employed to conduct all statistical analyses.

3 | RESULTS

Ten patients diagnosed with RRMM underwent treatment with talquetamab before transitioning to BCMA-based therapy. In this patients' cohort, five (50%) were male. Six (60%) were of African American descent, with the remaining 40% being non-Hispanic Caucasians. At the time of initiation of BCMA therapy post-progression with talquetamab, seven patients had an Eastern Cooperative Oncology Group (ECOG) performance status score of 1, and three had a score of 2. Half of the patients (50%) had extramedullary disease post-progression with talquetamab treatment. The median age of the cohort was 71 years (range: 59–81 years), and they had undergone a median of 6 prior lines of therapy, varying between 5 and 12. Nine patients (90%) had undergone prior autologous hematopoietic stem cell transplant. Of note, two patients had previously been treated with BCMA-targeted therapy, specifically belantamab mafodotin prior to the use of talquetamab. A positron emission tomography scan revealed that six patients had more than three focal bone lesions. Eight patients (80%) had penta-refractory disease (received at least two PIs, two IMiDs, and one anti-CD38 antibody). All participants experienced progressive disease before initiating talquetamab treatment and also at the time of initiation of BCMA-based therapy post-talquetamab. The demographic and baseline characteristics of the 10 patients are summarized in Table 1.

Out of the 10 patients who received the first BCMA therapy post talquetamab, four patients received belantamab mafodotin (BCMA ADC), three patients received BCMA CAR-T cells (idecabtagene vicleucel), and two patients received teclistamab (BCMA BsAb). One patient received ABBV-383 (with pomalidomide and dexamethasone), a BCMA-targeted IgG4 bispecific antibody. Three patients further received a second BCMA agent post talquetamab after progression with the first BCMA-based therapy, among them two patients received teclistamab and one patient received CAR-T (idecabtagene vicleucel) as the second BCMA agent.

In this case series of 10 patients, the ORR for talquetamab was 60% and the median PFS was 4 months (range: 1–15 months). For

TABLE 1 Patient baseline characteristics at the initiation of first B-cell maturation antigen (BCMA) therapy after talquetamab.

Characteristic	Frequency
Age at diagnosis, year, median (min–max)	61 (56–75)
Age at first BCMA therapy, year, median (min–max)	71 (59–81)
Gender, *n* (%)	
Male	5 (50)
Female	5 (50)
Race, *n* (%)	
White	4 (40)
Black	6 (60)
R-ISS at diagnosis, *n* (%)	
1	3 (30)
2	5 (50)
3	2 (20)
Myeloma subtype, *n* (%)	
IgG	6 (60)
IgA	1 (10)
Light chain	3 (30)
Eastern Cooperative Oncology Group Performance, *n* (%)	
1	7 (70)
2	3 (30)
Cytogenetics, *n* (%)	
High risk	6 (60)
Standard risk	4 (40)
Plasma cell leukemia, *n* (%)	0
Triple refractory[a], *n* (%)	10 (100)
Penta refractory[b], *n* (%)	8 (80)
Number of prior lines of therapy, median (min–max)	6 (5–12)
Number of prior stem cell transplants, *n* (%)	
0	1 (10)
1	5 (50)
2	1 (10)
3	2 (20)
5	1 (10)
PET scan ≥ 3 focal lesions, *n* (%)	6 (60)
Extramedullary disease (EMD), *n* (%)	5 (50)
Serum creatinine (mg/dL), median (min–max)	1.3 (0.7–1.6)
Hemoglobin (g/dL), median (min-max)	10.4 (8.8–12.4)
Absolute neutrophil count (x 10^3/μL), median (min–max)	2.85 (0.3–3.4)
Absolute lymphocyte count (x 10^3/μL), median (min–max)	0.98 (0.02–2.37)

(Continues)

TABLE 1 (Continued)

Characteristic	Frequency
Platelet count (x 10^3/μL), median (min–max)	154 (18–257)

Abbreviations: BCMA, B-cell maturation antigen; IgG, immunoglobulin G; IgM, immunoglobulin M; PET, positron emission tomography; R- ISS, Revised International Staging System.

[a]At least 1 proteasome inhibitor, 1 immunomodulatory drug, and 1 anti-CD38 antibody.

[b]At least 2 proteasome inhibitors, 2 immunomodulatory drugs, and 1 anti-CD38 antibody.

the first BCMA therapy post talquetamab, the overall response rate was 60%. Five out of 10 patients achieved a partial or complete response at 3 months, and one more patient achieved a response by 6 months. Four patients had progression at 3 months, three out of these had received belantamab mafodotin and one had received teclistamab. At the data cutoff date, the median follow-up was 9.5 months (ranging from 6 to 24 months), and the median PFS was 5.5 months (range: 1–10 months). Three patients who received the first BCMA agent post-talquetamab have not progressed yet (Figure 1).

Out of the four patients who did not achieve a response with prior talquetamab, two were able to obtain very good PR (VGPR) with the next BCMA agent, while the remaining two had progression by 3 months without achieving a response. Similarly, out of the six patients who achieved a response with prior talquetamab, four had responses with the next BCMA therapy while two did not achieve a response. The two patients who had received belantamab mafodotin prior to talquetamab both responded with the new BCMA targeted agent. Out of the five patients who had EMD prior to initiation of the first BCMA agent, only one patient had a resolution of EMD after the BCMA therapy. All three patients receiving a second BCMA agent had EMD prior to initiation of therapy, and two of them had resolution of EMD after therapy. The course of treatment and responses are summarized in Table 2.

Talquetamab mainly resulted in low-grade CRS and ICANS, mostly in grades 0–1. Subsequent treatments like CAR-T therapy, teclistamab, ABBV-383 with pomalidomide, and belantamab mafodotin showed diverse CRS and ICANS grades, ranging from low to absent events. Patient 6, despite low CRS with talquetamab, had higher-grade ICANS with BCMA CAR-T therapy, that resolved within 24 h after dexamethasone and tocilizumab. Patient 9 experienced grade 3 ICANS with teclistamab following mild talquetamab treatment and was eventually discharged to hospice. Overall, transitioning between therapies

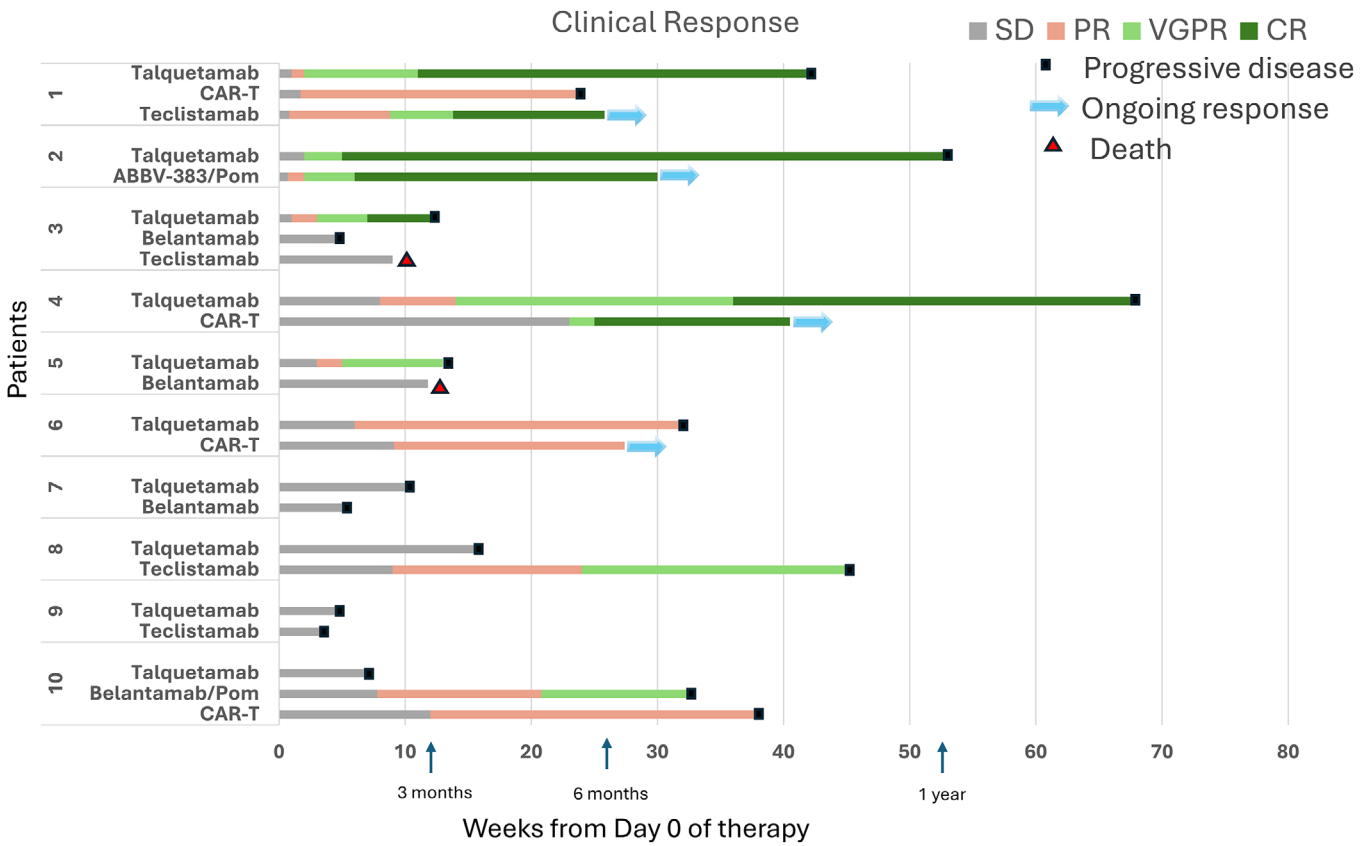

FIGURE 1 Swimmer's plot of clinical responses over time for talquetamab (T), first B-cell maturation antigen (BCMA) agent post talquetamab (B1), and second BCMA agent post talquetamab (B2). CR, complete response; PR, partial response; SD, stable disease; VGPR, very good partial response.

TABLE 2 Treatment sequence and responses.

No.		Best response	First BCMA post talquetamab	Best response	Response in 3 months	Response in 6 months	Prior EMD	EMD post therapy	Second BCMA post talque-tamab	Best Response	Response in 3 months	In 6 months	Prior EMD	EMD post therapy
1[a]	Talquetamab	sCR	CAR-T	CR	PR	PD	X	X	Teclistamab	VGPR	VGPR	**CR**[b]	X	–
2	Talquetamab	sCR	ABBV-383 + pomalidomide	sCR	sCR	**sCR**[b]	X	–						
3	Talquetamab	CR	Belantamab mafodotin	PD	PD		–	–	Teclistamab	SD	PD	Death	X	X
4	Talquetamab	CR	CAR-T	sCR	SD	**CR**[b]	–	–						
5	Talquetamab	VGPR	Belantamab mafodotin	SD	PD		X	X						
6	Talquetamab	PR	CAR-T	PR	PR	**PR**[b]	–	–						
7	Talquetamab	SD	Belantamab mafodotin	PD	PD		X	X						
8[a]	Talquetamab	SD	Teclistamab	VGPR	PR	VGPR	–	–						
9	Talquetamab	SD	Teclistamab	SD	PD		–	–						
10	Talquetamab	PD	Belantamab mafodotin /pomalido-mide/dexamethasone	VGPR	PR	VGPR	X	X	CAR-T	PR	PR	PR	X	–

Abbreviations: BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T; CR, complete response; N/A, not available; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease.; VGPR, very good partial response.

[a]Indicates the patient has received BCMA agents prior to talquetamab.

[b]Indicates ongoing response.

showed varied CRS and ICANS profiles in the patient group. A summary of CRS and ICANS data along with other AEs is available in Supporting Information.

4 | DISCUSSION

Our study investigated 10 patients who got talquetamab followed by BCMA-based treatments. Sixty percent responded to the first BCMA therapy after talquetamab. Belantamab mafodotin alone post-talquetamab showed poor responses (two progressions, one stable disease prior to progression), but combining it with pomalidomide and dexamethasone resulted in VGPR for one patient. Better responses were seen with BCMA bispecific antibodies (teclistamab and ABBV-383) after talquetamab. All CAR-T therapy post-talquetamab showed favorable response, among them one patient eventually had progression in 6 months. Two of the four patients who were not able to achieve a response with prior talquetamab, later had favorable outcomes with the next BCMA agent, suggesting that multiple subsequent BCMA-based therapies can be considered for patients not responding to talquetamab. Side effects varied: some had similar CRS and ICANS, while others experienced differing levels compared to talquetamab. This suggests that patients might still develop such important AEs with BCMA-based therapies regardless of prior AEs related to talquetamab. Notably, other AEs seen with talquetamab didn't reoccur with subsequent BCMA therapies for some patients.

Our study's median PFS of 5.5 months was lower than that reported in other studies that evaluated sequential therapies for RRMM. In a case series by Cohen et al., out of 20 heavily treated RRMM patients (median 8 lines of prior treatment), who were treated with BCMA CAR-T cell and previously received noncellular anti-BCMA immunotherapy (ADC or BsAb), the ORR was 60% and median PFS was 9.1 months [7]. Mouhieddine et al. studied 28 patients who had T cell redirection after treatment with BsAb. Nineteen patients received T cell redirection as their first salvage treatment with good outcomes—a median PFS1 of 28.9 months and 84% ORR. Ten patients received it as a second salvage treatment, with a PFS2 of 30.9 months. Note that, 82% of patients had BsAb targeting GPRC5D, but their specific outcomes weren't detailed [8]. The lower PFS seen in our study compared to other studies could be due to the limited number of patients, shorter follow-up period, and/or more heavily pretreated patient population.

Our study suggests that it is feasible to use multiple subsequent GPRC5D and BCMA-based therapies. With the emergence of talquetamab as a promising therapy, understanding patients' responses to subsequent therapies post-talquetamab progression is crucial. Despite limitations due to a small patient cohort and heterogenous BCMA therapy modalities, our study highlights the feasibility and response patterns of such sequencing and the necessity for further investigations into sequencing therapies following talquetamab progression.

AUTHOR CONTRIBUTIONS

Samer Al Hadidi conceived the research idea. Asis Shrestha collected the patient's data and wrote the initial draft. All authors contributed to data analysis, manuscript writing, and approval of the final version of the submission.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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No funding was received for this work.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article. Data are available on request due to privacy/ethical restrictions.

ETHICS STATEMENT

The authors have confirmed ethical approval statement is not needed for this submission.

PATIENT CONSENT STATEMENT

The authors have confirmed patient consent statement is not needed for this submission.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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