The changing spectrum of infection with BCMA and GPRC5D targeting bispecific antibody (bsAb) therapy in patients with relapsed refractory multiple myeloma


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Title: The changing spectrum of infection with BCMA and GPRC5D targeting bispecific antibody (bsAb) therapy in patients with relapsed refractory multiple myeloma

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Clinical Trials details: Clinical trials included in this study were performed at the Medical college of Wisconsin, University of Arkansas for Medical Sciences or Columbia University and included the use of single agent BCMA targeting bispecific antibodies (bsAbs), single agent GPRC5D targeting bsAbs or a combination of GPRC5D targeting bsAbs with daratumumab and/or pomalidomide (including NCT04634552, NCT04998747, NCT05050097, NCT04083534).

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Abstract

There is a paucity of granular data on infection risk with BCMA and GPRC5D bispecific antibodies (bsAb) in RRMM. The aim of our multi-institutional study was to characterize the incidence, etiologies, and risk-factors of infections from the start of therapy to the last follow-up or 90 days after study exit. A total of 66 patients received BCMA bsAb monotherapy, 15 GPRC5D bsAb monotherapy (GPRC5D-mono), and 15 GPRC5D bsAb combination therapy with daratumumab and/or pomalidomide (GPRC5D-combination). While the infection rate per 100 days was 0.57 for BCMA bsAb, it was 0.62 for GPRC5D bsAb-combination and 0.13 for GPRC5D bsAb-mono; \( p=0.05 \). The proportion of infections that were \( \geq \) grade 3 was higher in the BCMA bsAb group compared to the GPRC5D groups (58% vs 36%; \( p=0.04 \)).

Grade 5 events were observed in 8% (n=8) of the patients, all treated with BCMA bsAb. The 9-month cumulative incidence of any grade of infection was similar in the BCMA and GPRC5D-combination groups (57% and 62%) and significantly higher than in the GPRC5D-mono group (16%), \( p=0.012 \). The cumulative incidence of \( \geq \) grade 3 infections was highest in the BCMA group reaching 54% at 18 months, \( p = 0.06 \). Multivariate analysis showed that BCMA bsAb therapy or GPRC5D-combination therapy, history of previous infections, baseline lymphopenia, and baseline hypogammaglobulinemia were significantly associated with a higher risk of grade \( \geq 3 \) infections. Our results indicate that BCMA bsAb and GPRC5D BsAb-combination therapies in RRMM are associated with higher cumulative incidence of infection and \( \geq \) grade 3 infection compared to GPRC5D bsAb-mono.
Introduction

Bispecific antibodies (bsAb) targeting various cell surface antigens such as B cell maturation antigen (BMCA), G protein–coupled receptor, family C, group 5, member D (GPRC5D) and Fc receptor homolog 5 (FcRH5) have demonstrated impressive clinical efficacy in relapsed/refractory multiple myeloma (MM) \(^1\text{-}^{12}\). In December 2022, teclistamab, one of the first-in-class BCMA bsAb was approved for patients with relapsed/refractory MM after \(\geq 4\) prior lines of therapy \(^1\). Additionally, there are several non-BMCA targeting bsAbs in the pipeline including talquetamab (GPRC5D), forimtamig (GPRC5D) and cevostamab (FcRH5). Furthermore, these drugs are being investigated in earlier lines of therapy and in combination with immunomodulatory agents (IMiD) and anti-CD38 monoclonal antibodies (NCT05137054, NCT05090566, NCT05730036) NCT05020236, NCT04108195).

There are emerging reports of the changing spectrum of infections associated with the use of bsAb, including the risk of severe infection and infection-related death with this class of drugs. Thus far, the vast majority of these reports have focused on BCMA targeting bsAb \(^1,4,13\). Several factors compound the increased risk of infection in this particular drug class in addition to pre-existing host and disease related immunosuppression seen in RRMM \(^14\). Currently, this class of drugs is approved specifically after exposure to anti-CD38 monoclonal antibodies which by itself causes hypogammaglobulinemia and immunosuppression\(^15\). Furthermore, BCMA targeting bsAb cause almost universal profound and prolonged hypogammaglobulinemia, cytopenias (neutropenia and lymphopenia)\(^1\) and T-cell exhaustion especially with continuous therapy \(^16,17\). Additionally, the global coronavirus disease 2019 (COVID19) pandemic, the lack of universal uptake and availability of COVID19 vaccination, and the suboptimal response to the vaccine specifically in BCMA-directed therapy also contribute to infectious mortality \(^18,19\). Currently, there are no consensus guidelines on the optimal monitoring and prophylaxis of infections with this class of agents, neither in clinical trials nor on FDA prescribing guidelines for recently approved teclistamab.
While there are several early reports of infection risk with these agents, they are limited by lack of granular individual patient-level data on type of infections, risk-factors, and trajectory along the course of treatment. Furthermore, there is a gap in current knowledge whether non-BCMA targeting bsAbs lead to similarly high incidents of infections. The main objective of this study is to characterize the infectious complications and identify factors contributing to risk of infections in relapsed refractory MM patients treated with BCMA or GPRC5D bsAb therapies on early phase clinical trials at 3 academic institutions in the US.

**Methods**

**Patients and Disease Variables**

Patients in this study had relapsed refractory MM and were treated with either BCMA or GPRC5D bsAb therapy between November 2017 and September 2022 in various phase I/II clinical trials in 3 academic centers in the US, Medical College of Wisconsin, Milwaukee, WI, University of Arkansas for Medical Sciences, Little Rock, AR, and Columbia University Irving Medical Center, New York, NY. Patients receiving at least one dose of the study drug as single agent or in combination with other agents (daratumumab and/or pomalidomide) in the setting of a clinical trial were included. Eligibility criteria were similar across all trials and included RRMM patients with prior exposure to an anti-CD38 monoclonal antibodies, proteasome inhibitor (PI) and IMiDs with adequate blood counts (ANC> 1000/μl) and preserved organ function. All clinical trials also specifically excluded patients with an active infection. Data including patient demographics, disease characteristics (including bone marrow biopsy, fluorescence in situ hybridization studies, novel imaging positron emission tomography – computed tomography [PET-CT] at the most recent assessment before starting treatment were retrospectively collected. Immunoglobulin levels were obtained at baseline prior to study enrollment and repeated at day 1 of every cycle of treatment protocol. Functional IgG and IgA levels were computed by subtracting serum M-protein values from the affected total immunoglobulin value. The study was approved by the Institutional Review Board of the coordinating institution
(Medical College of Wisconsin) and subsequently by all participating institutions. The research was performed in compliance with the terms of the declaration of Helsinki. Data cutoff was December 31st, 2022.

Supportive care, infection prevention and monitoring

Supportive care, infection prevention and monitoring strategies were implemented according to institutional guidelines. All patients were on antimicrobial prophylaxis with acyclovir or valacyclovir. Prophylactic use of intravenous immunoglobulin (IVIG) or primary Pneumocystis jiroveci pneumonia (PJP) prophylaxis was not implemented because there was no convincing data to support their use at start of these trials. Similarly, routine pharmacological prophylaxis or generalized monitoring of CMV was not employed. Neutropenic precautions with antibiotics and antifungal agents were administered at the discretion of the treating physician or according to institutional guidelines, if applicable. The decision to administer granulocyte colony stimulating factor was directed by the absolute neutrophil count. Serum immunoglobulin (IgG, IgM and IgA) concentration was evaluated before starting therapy and repeated on a monthly interval. Intravenous immunoglobulin replacement was administered if the serum IgG concentration was ≤ 400 mg/dL or at the discretion of treating physician or institutional guidelines as applicable.

Infection categorization

Infections confirmed by clinical, imaging, microbiological, or histopathological evidence were captured from day 1 of the first cycle of bsAb until the last follow-up or 90 days after completion of the study. Since bsAb therapy can lead to depletion of endogenous plasma cells including long lived plasma cells, we collected infection data for an extended period of 90 days after completion of study. The National Cancer Institute Common Terminology Criteria for Adverse Events, version 5, was used to describe the site and degree of infections.20

Results

Patients and treatment characteristics
For this study, 96 treatment occasions from 90 patients were included. Among these, BCMA and GPRC5D bsAb were used in 66 and 30 treatment occasions, respectively. Fifteen patients received GPRC5D bsAb combination therapy with IMiD and anti-CD38 monoclonal antibody and 15 received GPRC5D bsAb therapy as a single agent. The baseline characteristics of the patients included in this study are summarized in Table 1. The overall median age was 69 (range 45-91) years and 46% (n=44) were female with no significant differences between groups. Ethnicity and race differed slightly between the groups, with a higher representation of Blacks in the GPRC5D bsAb monotherapy group and higher prevalence of Hispanics in the BCMA bsAb group, p=0.05. Disease and prior treatment specific characteristics were similar across all groups: IgG Kappa (40%; n=38) was the most common subtype of MM and 97% (n=93) were triple class exposed. The patients were heavily pre-treated with 5 (range 2-11) prior lines of therapy and 86% (n=82) had prior autologous stem cell transplant (ASCT) including 37% (n=34) a second ASCT. The use of tocilizumab for CRS (BCMA bsAb=34%, GPRC5D bsAb combination=60% vs GPRC5D bsAb monotherapy=40%; p=0.2 ) and steroids for the management of CRS/ICANS (BCMA bsAb=17%, GPRC5D bsAb combination=27% vs GPRC5D bsAb monotherapy=6.7%; p=0.3) was similar across all groups. Baseline immune function was equally similar in all groups with no significant differences. The median absolute neutrophil counts at the start of treatment were 3 (range 1.0-10.8) x10^3/µL and the median lymphocyte counts was 0.65 (range 0.01-4.82) x10^3/µL. Of interest is that IVIG use during bsAb therapy was significantly higher in the BCMA bsAb and GPRC5D bsAb combination groups compared to GPRC5D bsAb monotherapy group, p=0.01.

**Incidence and Etiology of Infections**

The median follow up was 193 days for the entire cohort. The median days at-risk were 160 (range 27-795), 169 (range 92-590) and 224 (43,336) for the BCMA bsAb, GPRC5D bsAb
combination and GPRC5D bsAb monotherapy groups, respectively. A total of 127 infections were diagnosed during the 96 at-risk periods in 90 patients, Figure 1. Amongst these, 99 infectious events occurred in recipients of BCMA bsAb (mean infection rate= 1.5/patient), 24 with GPR5D bsAb combination (mean infection rate= 1.6/patient) and 4 in GPRC5D bsAb monotherapy (mean infection rate=0.27/patient), \( p=0.06 \). The infection rate per 100 days was 0.57 for BCMA bsAb, 0.62 for GPRC5D bsAb combination, and 0.13 for GPRC5D bsAb monotherapy; \( p=0.055 \). The proportion of \( \geq \) grade 3 infections were higher in BCMA bsAb treated patients (58%) compared to those treated with GPRC5D bsAb combination (33%) or monotherapy bsAb (50%), \( p=0.06 \), Table 2. Similarly, the need for hospitalization was higher in the BCMA bsAb group (74%) compared to GPRC5D bsAb single (50%) or combination therapy (54%), \( p=0.07 \). Infection related deaths (grade 5) occurred only in the BCMA bsAb group (8.2%).

**Cumulative Incidence of infections**

When looking at the dynamics of the infection rates, we saw a steep increase of cumulative incidence within the first 6 months for patients treated with BCMA bsAb (55%) or GPRC5D bsAb combination therapy (62%) with a continuous, but slower increase of cumulative incidences until 18 months (BCMA bsAb = 69% and GPRC5D bsAb combination =70%), Figure 2A. In contrast, the cumulative incidence of infections was significantly lower in patients treated with single-agent GPRC5D bsAb at all time-points with a 9-month cumulative incidence of 16%, \( p=0.012 \). Severe infections (\( \geq \)grade 3) followed a similar pattern with a rapid increase of cumulative incidence until 6 months for the BCMA bsAb (33%) and GPRC5D bsAb combination (34%) groups, followed by a slower increase in BCMA bsAb treated patients (54%) and leveling off for patients treated with GRPC5D bsAb (34%) by 18 months, Figure 2B. Patients receiving GPRC5D bsAb monotherapy again had a lower cumulative incidence of severe infections (7.1% at 9 months), \( p= 0.058 \), with all of them occurring in the first 3 months.
Infectious Spectrum of bsAb therapy

The distribution and rates of bacterial, viral, and fungal infection were similar across the 3 groups. Of the total number of infections in BCMA BsAb group (n=99), the incidence of bacterial, viral, and fungal infections was 54%, 39%, and 7% respectively. Of the 28 infectious episodes in the GRPC5D BsAb group, the incidence of bacterial, viral, and fungal infections was 50%, 38%, and 12%, respectively. Bacterial infections appeared to be more common in the BCMA bsAb group and GPRC5D bsAb-combination group with 54% and 50% of all infections respectively, compared to GPRC5D bsAb-monotherapy (25%), albeit this observation was non-significant. Of the 4 infections in the GPRC5D bsAb monotherapy group, 1 was bacterial and 3 were viral. A detailed description of some of the representative infections are as follows. Among the bacterial infections, bacteremia was observed in 24.4% of patients (31 cases; 27 with BCMA bsAb and 7 with GPRC5D bsAb combination therapy). The pathogens implicated in bacteremia in this cohort include *Pseudomonas aeruginosa*, *Capnocytophaga species*, *Streptococcus species*, *Helicobacter canis*, *Campylobacter jejuni*, *Escherichia coli*, *Enterococcus faecium*, *Rhizobium radiobacter*, and *Ochrobactrum anthropic*. A case of *pseudomonas aeruginosa* bacteremia with secondary purulent bacterial pericarditis developed in a patient with profound hypogammaglobulinemia (IgG levels of < 40 mg/dL) after being on BCMA bsAb therapy for 12 months. Interestingly, poly microbial central-line associated blood stream recurrent infection with *Ochrobactrum anthropi* and *Rhizobium radiobacter* occurred in a patient after 5 months of BCMA bsAb therapy and required prolonged antibiotic therapy. There were 12 cases (9.4%) of pneumonia in this cohort including 3 cases of PJP and 2 cases of *Aspergillus species*. All three patients were not receiving primary PJP prophylaxis. One patient was found to have a “proven” Aspergillus infection through a positive sputum culture, while another patient showed “probable” Aspergillus infection with a nodular consolidation in the lungs, as well as a positive galactomannan test on bronchoalveolar lavage (BAL). We also note a case of necrotizing
fasciitis and gangrenous cholecystitis, both in recipients of BCMA bsAb. Three patients in this cohort, all recipients of BCMA bsAb therapy, had Cytomegalovirus (CMV) viremia without any associated end organ disease. We also report a case of prolonged and severe norovirus diarrhea that lasted more than 6 months in a patient treated with BCMA bsAb after being on therapy for almost a year. It is noteworthy that this occurred in the setting of hypogammaglobinemia while receiving IVIG with IgG levels ranging between 300-400 mg/dL and with profound lymphopenia with absolute lymphocyte counts ranging between 0.06-0.53 x 10^3/uL. This case of recalcitrant norovirus infection was treated with nitazoxanide, oral human serum immunoglobulin and stem cell boost for immune reconstitution along with supportive care. This patient was finally taken off therapy due to infectious complications. In this cohort, there were 24 cases (18.9%) of COVID19 infection, 17 in BCMA bsAb, and 5 with GPRC5D bsAb combination and 2 with GPRC5D bsAb monotherapy.

Severity of infection

Infections during GPRC5D bsAb therapy were more likely to be grade 1 or 2 compared to that with BCMA bsAb (65% vs 42% respectively; p=0.023) (Table 2). The 18-month cumulative risk of ≥ grade 3 infection BCMA bsAb was higher at 54% (95% CI 42%-87%), compared to 21% (95%CI 10%-42%) with GPRC5D bsAb (p=0.03). Of note, there were 8 (8%), grade 5 events, all observed in recipients in BCMA bsAb therapy. The grade 5 events included severe sepsis with Candida glabrata empyema (n=1), severe COVID19 infection and multiorgan failure (n=1), severe sepsis with Pseudomonas bacteremia (n=1), severe sepsis and multiorgan failure (n=2) severe sepsis with Enterococcus faecalis bacteremia (n=1), septic shock secondary to Escherechia Coli bacteremia (n=1), and combination of acute respiratory distress syndrome with septic shock secondary to concurrent PJP with Pseudomonas bacteremia (n=1). In general, 85 infection events (BCMA bsAb: 70 and GPRC5D bsAb :15; p=0.07) required hospitalization in this cohort.
Clinical characteristics associated with an increased risk of infection.

In a last step we attempted to determine factors associated with the risk of overall and ≥grade 3 infections. In a multivariable Cox-regression model for risk-factors of all-grade infection, with single-agent BCMA bsAb as a reference, GPRC5D bsAb monotherapy had a significantly lower risk (HR 0.14; 95% CI, 0.02-1.03) of infections while there was no significant difference with GPRC5D bsAb combination therapies (HR 1.36; 95% CI, 0.86-2.16), p=0.006. A history of previous infections on bsAb therapy was a significant risk factor for subsequent infections in multivariate analysis (HR 1.3; 95% CI, 1.12-1.52; p=0.001). For grade ≥3 infection, with single-agent BCMA bsAb as a reference, GPRC5D bsAb monotherapy (HR 0.00; 95% CI, 0.00-NR) and GPRC5D bsAb combination therapies (HR 0.66; 95% CI, 0.30-1.42) both had a significantly lower risk (p=0.014). Additionally, history of prior infections on bsAb therapy (HR 1.32; 95% CI, 1.07-1.63; p=0.012), baseline lymphopenia (HR 1.4; 95% CI, 0.98-2.04; p=0.016) and hypogammaglobinemia (IgG <400 mg/dL) at the start of therapy (HR 1.4; 95% CI, 1.11-1.80; p=0.012) were associated with significantly higher risk of grade ≥3 infections.

Discussion

In this study, we report that infection related toxicities are a significant burden in patients with RRMM who were treated with bsAb. The risk of infection varies depending on bsAb therapy. Patients receiving single agent BCMA-targeting bsAb had a higher risk of overall and grade ≥3 infections compared to those receiving GPRC5D bsAb monotherapy. However, infection risk increased with GPPRC5D bsAb therapy when combined with daratumumab and /or pomalidomide. The increased risk of infections in combination group was evident despite a higher use of IVIG , suggestion that IVIG therapy may not fully mitigate the infection risk. The study also highlighted a changing spectrum of infections including rare opportunistic infections, viral reactivation syndromes, and fungal infections. The cumulative incidence of grade ≥ 3 infections increased with time on therapy with highest incidence at 18 months in the BCMA
bsAb group. The most common etiology of infections was bacterial followed by viral and fungal. Additionally, the study found that target antigen, number of prior infections on bsAb therapy, baseline lymphopenia and hypogammaglobulinemia were independent risk factors for ≥ 3 infections.

Putative drivers of immunosuppression that lead to increased infection risk with bsAb include hypogammaglobulinemia, cytopenia (especially neutropenia and lymphopenia), and T-cell exhaustion. Hypogammaglobulinemia is an on-target off-tumor toxicity of bsAb due to the presence of the target antigens (BCMA) \(^{21}\) and GPRC5D \(^{22}\) in both malignant and normal plasma cells, leading to profound plasma cell ablation. In particular, BCMA is essential for the survival of long-lived plasma cells, which is a key player in maintaining humoral immunity \(^{23}\). Compared to BCMA, GPRC5D expression on normal plasma cells is minimal, which may theoretically lower the occurrence of hypogammaglobulinemia associated with GPRC5D targeting therapies in MM \(^{22}\). This could plausibly explain the lower rates of infection we noted with GPRC5D monotherapy. Additionally, 97% of patients in our study were triple class exposed, indicating prior exposure to anti-CD38 monoclonal antibody, which are also associated with prolonged hypogammaglobulinemia \(^{24,25}\). The MajesTEC-1 study that led to the approval of BCMA bsAb, teclistamab, reported a hypogammaglobulinemia incidence of 75% \(^{1}\). In our study, a baseline hypogammaglobulinemia was also associated with 1.4-fold higher risk of ≥ grade 3 infections, Primary prophylaxis with immunoglobulin supplementation in patients with a low baseline functional IgG level to mitigate infection risk should be further tested.

Baseline lymphopenia was another significant predictor of high-grade infections in our study. Of note, 3/90 patients (3.3%) developed PJP, which is comparable to the PJP incidence seen with teclistamab in MajecTEC-1 trial (3.6%) \(^{1}\), and highlights the importance of prophylaxis. T-cell exhaustion may also be an important driver of immunosuppression with bsAb, especially in the context of indefinite therapy \(^{26,27}\). and could be mitigated with treatment-free intervals as previously shown \(^{26}\). Since infections associated with T-cell immunosuppression such as PJP,
CMV, and fungal infections have been documented with bsAb, future studies should test fixed-duration treatment or treatment-free intervals to potentially mitigate infection risk without sacrificing efficacy. In the present manuscript, we share our encounter with infection complications in the early clinical trials when routine infectious disease monitoring and prophylaxis such as PJP prophylaxis were not implemented in a uniform fashion. However, we have since taken proactive measures, including IVIG replacement and adjusting PJP prophylaxis based on CD4 counts, while waiting for prospective data. These changes are expected to reduce the burden of infections.

The target antigen and the use of the combination regimen were shown to modulate the risk of infection in our study. In a pooled analysis of trial-level data from 11 clinical trials testing single-agent BCMA, GPRC5D, or FcRH5 bsAb, non-BCMA bsAb were shown to have lower incidence of grade 3/4 infection compared to BCMA bsAb (12% vs 30% respectively; p=0.01) which is consistent with our findings that GPRC5D bsAb therapy had a lower infection burden overall. Although a total of 28 of 1185 patients in their study (2.4%) had infection-related deaths, the distribution of these events by target bsAb was not specified. In our study, infection-related death was observed in 8 out of 90 patients (8.9%), all of which were in patients who had received BCMA bsAb. In a small study of 39 patients receiving bsAb therapy, predominantly GPRC5D bsAb, 90% of cases experienced infections, with 40% being grade 3 or higher, primarily originating from the respiratory tract and commonly caused by viral etiologies. It is important to note that the study did not specify whether GPRC5D was used as a monotherapy or in combination with other treatments. Notably, 2/32 patients (6.3%) in MajesTEC-2 study testing teclistamab in combination with daratumumab and lenalidomide had fatal infections. As we bring bsAb into clinical trials in earlier lines of therapy, especially in combination regimens, randomized design should be employed early on since single-arm trials can potentially miss an increased death signal from infections.
In clinical trials of autologous BCMA CAR-T cell therapy, the infection rates have varied between 42% and 69%. Specifically, grade ≥3 infections were reported in 22% of study subjects treated with ide-cel and 23% with ciltacabtagene autoleucel (cilta-cel) in the registrational studies. A recent real-world report showed that infections were observed in 34% of patients treated with ide-cel, with bacterial infections being the most common (20%), followed by viral infections (16%) and fungal infections (1%)\textsuperscript{31}. GPRC5D CAR T-cell therapy was associated with an overall infection rate of 18%, with 12% of these being grade ≥3 infections\textsuperscript{32}. In our previous report, we observed a higher cumulative incidence of infection and infection density among recipients of BCMA BsAb therapy when compared to BCMA CAR T therapy\textsuperscript{33}. However, it is important to note that the study had several limitations, including a short follow-up period, fewer prior lines of treatment, and less heavily pretreated patients in the CAR T therapy group compared to the BsAb group. It is reasonable to consider that continuous therapy, particularly with BCMA bispecific antibody (bsAb) therapy, is more likely to result in significant hypogammaglobulinemia compared to CAR T therapy, which is a one-time treatment. This increased hypogammaglobulinemia could potentially elevate the risk of infections. It is important to note that another significant factor limiting direct comparisons is the implementation of routine primary PJP and IVIG prophylaxis post CAR T therapy, whereas no prophylaxis was implemented in the described BsAb therapy group. This difference in prophylactic measures makes any direct comparison between the two treatments limited in its interpretability.

Our study has limitations. First, the current report is a retrospective analysis of patients enrolled in early phase trials and treated at varying doses and frequencies of bsAb. Second, infection prophylaxis and monitoring strategies were not standardized at our institutions during the time-period of patient enrollment in these trials, with practice varying according to the treating physician. Third, our follow-up was short. It is unclear whether the risk of infection continues to increase or there is a plateau in incidence after a certain time point. Taken together, infection-related morbidity and mortality is a clinically significant adverse effect of bsAb in MM.
Given the available data, practical recommendations for monitoring and prophylaxis of infections have been published\textsuperscript{34,35}. While waiting for robust data generated by clinical trials, it is now highly recommended to maintain a high level of vigilance by implementing routine antibacterial prophylaxis during the first month of therapy\textsuperscript{34}. Additionally, for all patients undergoing bsAb therapy, primary IVIG and PCP prophylaxis are recommended\textsuperscript{34}.

In conclusion, infection-related morbidity and mortality is a clinically significant adverse effect of bsAb in multiple myeloma. Research on strategies to mitigate infection risk, including prophylaxis, fixed-duration treatment, and treatment-free intervals are urgently needed. Our study corroborates previous reports showing a high risk of infection with BCMA targeting bsAb therapy. We further show that GPRC5D bsAb therapy has a significantly lower risk of infections compared to BCMA therapy. Combination GPRC5D bsAb therapy raises the overall infection rates to comparable levels of BCMA therapy, albeit the severity of infections (≥ grade 3) appears still higher in BCMA bsAb treated patients.


30. Searle E, Quach H, Wong SW, et al. Teclistamab in Combination with Subcutaneous Daratumumab and Lenalidomide in Patients with Multiple Myeloma: Results from One Cohort of MajesTEC-2, a Phase1b, Multicohort Study. Blood. 2022;140(Supplement 1):394-396.


<table>
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<td>Prior lines of therapy</td>
<td>5.00 (2.00 - 11.00)</td>
<td>5.00 (2.00 - 11.00)</td>
<td>6.00 (2.00 - 10.00)</td>
<td>6.50 (3.00 - 10.00)</td>
<td>0.044^2</td>
</tr>
<tr>
<td>Prior autologous stem cell transplant</td>
<td>82 (86%)</td>
<td>54 (83%)</td>
<td>14 (93%)</td>
<td>14 (93%)</td>
<td>0.5^4</td>
</tr>
<tr>
<td>CRS grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.006^4</td>
</tr>
<tr>
<td>0</td>
<td>34 (35%)</td>
<td>28 (42%)</td>
<td>1 (6.7%)</td>
<td>5 (33%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ICANS grade</td>
<td>0 (95%)</td>
<td>1 (1.0%)</td>
<td>2 (4.2%)</td>
<td>IVIG supplementation</td>
</tr>
<tr>
<td>---</td>
<td>-------------</td>
<td>--------</td>
<td>----------</td>
<td>----------</td>
<td>----------------------</td>
</tr>
<tr>
<td>1</td>
<td>47 (49%)</td>
<td>27 (41%)</td>
<td>14 (93%)</td>
<td>6 (40%)</td>
<td>47 (49%)</td>
</tr>
<tr>
<td>2</td>
<td>13 (14%)</td>
<td>10 (15%)</td>
<td>0 (0%)</td>
<td>3 (20%)</td>
<td>33 (50%)</td>
</tr>
<tr>
<td>3</td>
<td>2 (2.1%)</td>
<td>1 (1.5%)</td>
<td>0 (0%)</td>
<td>1 (6.7%)</td>
<td>11 (73%)</td>
</tr>
</tbody>
</table>

ICANS grade: 0.032

<table>
<thead>
<tr>
<th>Median (Range); n (%)</th>
<th>Wilcoxon rank sum test</th>
<th>Pearson's Chi-squared test</th>
<th>Fisher's exact test</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.013</td>
<td>0.032</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* R-ISS staging available in 50 patients
/FISH data is not available in 21 patients.
±Data not available in 26 patients
¡Data not available in 25 patients
NA: Not available
Table 2: Characteristics of infectious events

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>BCMA, N* = 99</th>
<th>GPRC5D-combination, N* = 24</th>
<th>GPRC5D Monotherapy, N* = 4</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of total infections per 100 days</td>
<td>0.57 (0.08)</td>
<td>0.62 (0.26)</td>
<td>0.13 (0.13)</td>
<td>0.055\textsuperscript{b}</td>
</tr>
<tr>
<td>Rate of ≥ grade 3 infections per 100 days</td>
<td>0.33 (0.06)</td>
<td>0.21 (0.13)</td>
<td>0.06 (0.09)</td>
<td>0.10\textsuperscript{b}</td>
</tr>
<tr>
<td>Rate of bacterial infections per 100 days</td>
<td>0.31 (0.06)</td>
<td>0.31 (0.10)</td>
<td>0.03 (0.04)</td>
<td>0.065\textsuperscript{b}</td>
</tr>
<tr>
<td>Rate of viral infections per 100 days</td>
<td>0.22 (0.04)</td>
<td>0.23 (0.10)</td>
<td>0.10 (0.09)</td>
<td>0.4\textsuperscript{b}</td>
</tr>
<tr>
<td>Rate of fungal infections per 100 days</td>
<td>0.03 (0.01)</td>
<td>0.08 (0.07)</td>
<td>0 (0)</td>
<td>0.14\textsuperscript{b}</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.63\textsuperscript{2}</td>
</tr>
<tr>
<td>Bacterial</td>
<td>53 (54%)</td>
<td>12 (50%)</td>
<td>1 (25%)</td>
<td></td>
</tr>
<tr>
<td>Viral</td>
<td>38 (39%)</td>
<td>9 (38%)</td>
<td>3 (75%)</td>
<td></td>
</tr>
<tr>
<td>Fungal</td>
<td>7 (7.1%)</td>
<td>3 (12%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (1.0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.074\textsuperscript{3}</td>
</tr>
<tr>
<td>1</td>
<td>6 (6.1%)</td>
<td>2 (8.3%)</td>
<td>1 (25%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>35 (36%)</td>
<td>14 (58%)</td>
<td>1 (25%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Need for hospitalization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>--------------------------</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>37 (38%)</td>
<td>6 (25%)</td>
<td>2 (50%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>12 (12%)</td>
<td>2 (8.3%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>8 (8.2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>0.07</strong>&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>28 (29%)</td>
<td>13 (46%)</td>
<td>2 (50%)</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>70 (71%)</td>
<td>15 (54%)</td>
<td>2 (50%)</td>
<td></td>
</tr>
</tbody>
</table>

* N represents number of infectious events with a given bsAb

- <sup>1</sup>n (%)
- <sup>2</sup>Fisher's exact test
- <sup>3</sup>Wilcoxon rank sum test
- <sup>4</sup>Pearson's Chi-squared test
- <sup>5</sup>Quasi-Poisson regression
**Figure 1:** Swimmer plot of infections with BCMA and GPRC5D bispecific antibodies

**Figure 2:** Cumulative incidence of all and ≥ grade 3 infections with BCMA and GPRC5D bispecific antibodies. Figure 2A shows incidence of all grade and figure 2B ≥ grade 3 infection with BCMA and GPRC5D bispecific antibodies.
The figures show cumulative incidence of infection and Grade 3+ infection over time from the start of treatment, measured in months. The comparison groups are BCMA, GPRC5D combination, and GPRC5D single agent.

For infection:
- BCMA group (red line) is compared against GPRC5D combination (green line) and GPRC5D single agent (blue line).
- The p-value is 0.012, indicating a statistically significant difference.

For Grade 3+ infection:
- Similar groups are compared, with the p-value being 0.058, also indicating a statistically significant difference.

The y-axis represents the cumulative incidence percentage, while the x-axis shows the time from the start of treatment in months.
**Supplementary data:**

**Treatment**

Patients received bsAb therapy according to the study protocol. CRS and ICANS were graded according to the American Society for Transplantation and Cellular Therapy consensus. Management of CRS and ICANS were done according to specific clinical trial protocol.

**Qualitative variables and statistical methods**

Demographic and baseline clinical characteristics were summarized as counts with percentages for categorical measures, and median with range for continuous ones. Between-group comparisons of categorical variables were performed using chi-squared test, or Fisher’s exact test if any expected cell counts were below 5. Wilcoxon’s rank-sum test and Kruskal-Wallis test was used to compare ordinal and continuous measurements between two or multiple groups, respectively.

Descriptive statistics of infection characteristics were computed similarly, but survey-adjusted versions of tests were used to account for the correlation between multiple infections within the same patient. The person-level infection burden was summarized as the number of infections per 100 days at risk to account for varying follow-up. Quasi-Poisson regression with log-transformed number of days-at-risk as offset was used for between-group comparisons. The cumulative incidence of the first occurrence of an infection with treatment discontinuation / death as competing risk was estimated using the Aalen-Johansen estimator and compared between groups using Gray’s test. A day-level Cox proportional cause-specific hazards regression model was fitted to assess risk factors of infection. Evaluated covariates included demographics, disease characteristics at the start of first bsAb treatment, and the cumulative number of prior infections. The multivariable model was selected using AIC-guided backward selection, starting from the model that included all covariates included in the univariate analysis. The primary predictor of interest, bsAb type, was included in the model regardless of its effect on the AIC.