



Editorial

Volume 28 Issue 2 - January 2025  
DOI: 10.19080/CTOIJ.2025.28.556231

Cancer Ther Oncol Int J

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# Bispecific Antibodies in myeloma: How to Use?



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Submission: December 13, 2024; Published: January 07, 2025

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## Abstract

Bispecific antibodies (BsAbs) are antibody constructs having 2 different antigen binding sites. BsAbs are approved for the treatment of relapsed, refractory multiple myeloma (RRMM) patients after four previous lines of therapy including immunomodulatory drugs, proteasome inhibitors, and anti-CD38 monoclonal antibodies. The toxicities of BsAbs result from T-cell activation occurring after their administration and are quite similar between all the CD3-binding BsAbs. In addition to side effects specific for each type of BsAbs which are related to the difference in BsAbs design and its surface target antigen.

**Keywords:** Bispecific antibodies; GPRC5D; Cytokine release syndrome; Neurotoxicity; RRMM

**Abbreviations:** BsAbs: Bispecific antibodies; RRMM: relapsed, refractory multiple myeloma; CRS: cytokine release syndrome; GPRC5D: G-protein-coupled receptor family C group 5 member D

## Introduction

Bispecific antibodies (BsAbs) are novel promising anticancer treatment option for hematologic malignancies [1].

### What are BsAbs?

BsAbs are antibody constructs having 2 different antigen binding sites. They either bind 2 epitopes of the same antigen or 2 different antigens. They can also bind a tumor cell specific antigen on the targeted cancer cell and an immune effector cell (T-cell CD3 co-receptor) simultaneously [2]. Tri-specific antibodies (TsAbs) can either target an additional target antigen or a co-stimulatory protein to decrease T cell anergy [2]. BsAbs is distinguished from traditional monoclonal antibodies by their ability to target multiple antigens simultaneously and redirect immune effector cells such as T cells [3].

### What are the therapeutic targets on plasma cells?

BsAbs should target unique and specific antigen that is highly and uniformly expressed on plasma cells and is minimally or not expressed on healthy tissues for their maximal efficacy and minimal toxicity. Currently, the approved and in-trial BsAbs for multiple myeloma (MM) are directed against BCMA (B-cell membrane antigen), GPRC5D (G-protein-coupled receptor family C group 5 member D), FcRH5 (Fc receptor-homolog 5), and CD38

on the plasma cells. Other tumor specific antigens such as SLAMF7 and CD138 on plasma cells and effector cell targets like CD16a, NKp30, or NKG2D are still in the phase of therapeutic exploration [2].

The currently FDA-approved BsAbs for RRMM patients are teclistamab (an anti-BCMAxCD3 BsAb, tectivayli 2022), elranatamab (anti-BCMAxCD3 BsAb, elrexio 2023) and talquetamab (anti-GPRC5DxCD3, talvey™ 2023) [3]. They are approved for the treatment of relapsed, refractory multiple myeloma (RRMM) patients after four previous lines of therapy including immunomodulatory drugs, proteasome inhibitors, and anti-CD38 monoclonal antibodies [1]. They are administered either by i.v. or s.c. route. Less reported data is available about their efficacy in myeloma with extramedullary involvement or with high-risk cytogenetic abnormalities [1].

### What are the possible side effects of BsAbs?

BsAbs toxicities are partly resulting from T-cell activation occurring after their administration. They are quite similar between all the CD3-binding BsAbs [3]. Cytokine release syndrome, neurotoxicity (including immune effector cell-associated neurotoxicity syndrome), infections, and cytopenias are the most important adverse effects of BsAbs [4]. The rate of

hematological toxicity, CRS, and ICANS are generally equivalent amongst BsAbs [5]. In addition, a different set of side effects which are related to the difference in BsAbs surface target antigen and its design and are specific for each type of BsAbs [3]. For e.g. talquetamab has unique side-effects such as dysgeusia, nail and skin toxicity and weight loss that pose unique challenge to its early use in the disease course [4].

### T-cell activation -associated BsAbs toxicities

Cytokine release syndrome (CRS) of all grades is observed in 55%-80% of the RRMM patients. Grade 1 and 2 are the most commonly reported and grade  $\geq 3$  occurs in 0%-4% of patients. CRS occur mostly the day after s.c. BsAb administration. The syndrome consists of systemic inflammatory reaction resulting from the release of proinflammatory cytokines, such as interleukin-6. Fever ( $\geq 38^{\circ}\text{C}$ ) is an obligatory symptom. Additional symptoms are headache, nausea, chills, malaise, muscle aches, hypotension, hypoxia, and tachycardia. There is no relation between clinical efficacy of the BsAbs and the occurrence of CRS. In most schedules, one to two step-up doses are implemented before giving the full dose of BsAbs to alleviate the severity of CRS. In addition, glucocorticoid, an antihistaminic, and an antipyretic premedication are given to lower the CRS severity. CRS can develop after each step-up dose or after the full dose. It can even occur more than once in a single patient [3]. Cutaneous reactions at the injection site occur in approximately 20%-45% of the patients treated with s.c. BsAbs. They occur most frequently in the first 8 weeks of treatment. These reactions are managed with conservative measures and resolve within days after the injection [3]. Tumor flare is an immune reaction that present clinically as an increase in bone pain or swelling of an extramedullary lesion. It is not reported in the clinical trials in MM patients [3].

### Cytopenias

All BsAbs are associated with transient cytopenias in RRMM patients. This may be related to the suppression of hematopoietic cells maturation following the release of cytokines in the bone marrow microenvironment. Another factor is the poor bone marrow reserve before the start of BsAbs in many RRMM patients. In prospective trials, neutropenia is reported in 30%-75%, while anemia and thrombocytopenia are reported in 35%-60%, and in 25%-40% respectively of RRMM patients. Hematological toxicity  $\geq$  grade 3 is the most reported side effect with the BsAbs use [3].

### Infections

BsAbs are associated with an increased risk of infections. The rate and type of infections differ between BsAbs. The infection rate seems to be higher (70%-80%), with teclistamab and elranatamab treatment, compared with talquetamab (34%-47%). The high rate of infections in anti-BCMA BsAbs may be explained by immunosuppression due to neutropenia, T-cell exhaustion, B-cell

aplasia, impaired BCMA signaling, and the presence of profound hypogammaglobulinemia at the start the treatment [3]. The non-BCMA directed BsAbs, talquetamab result in a lower incidence of infections. This is likely because non-BCMA directed BsAbs spare terminally differentiated B-lymphocytes, than BCMA-directed BsAbs resulting in less B cell aplasia [5]. Before the availability of COVID-19 vaccinations, the major type of infections with anti-BCMA BsAbs was respiratory infections (non-COVID-19/nonpneumocystis jirovecii pneumonia [PJP]) and COVID-19 infections. Viral infections or reactivations, opportunistic infections such as PJP, fungal infections, and progressive multifocal leukoencephalopathy/PML were also seen. Grade 3/4 infections occurred in 40%-55% of the patients, and the fatality rate of these infections was 6.5% - 12.7%. With teclistamab, the median time to first onset of any-grade and grade 3-5 infections was 1.7 and 4.2 months, respectively.

### Prevention of infections

Before start of the BsAb therapy, vaccinate all RRMM patients, against varicella zoster (VZV), pneumococcal species, and yearly against influenza and COVID-19 and test for HIV, Hepatitis B and C, cytomegalovirus and EBV. Prophylaxis for PJP and herpes simplex virus/VZV, and antibacterial prophylaxis are recommended in RRMM patients especially when grade 3/4 neutropenia is present. Early IgG replacement therapy should be started in patient with IgG levels  $< 400$  mg/L [3]. Modifying the administration of maintenance schedule of BsAbs significantly influences infectious and myelosuppressive side effects [5]. There seems to be a reduction in grade  $\geq 3$  infections over time with less frequent teclistamab dose after 1 year [3]. Switching to a biweekly schedule with elranatamab (magnetisMM-3), teclistamab (NCT05932680) and talquetamab reduced the incidence of grade 3-4 adverse events particularly infections and myelosuppression while treatment responses is maintained [5].

### Immune effector cell-associated neurotoxicity syndrome (ICANS)

The syndrome consists of signs of diffuse encephalopathy such as diminished consciousness, tendency to fall asleep, disorientation, apraxia, limited daily living activities, and dysphasia. ICANS grade 1 or 2 has been reported in 3%-8% of myeloma patients. In most cases, ICANS develops together or after CRS occurrence. Delayed parkinsonian syndrome has not been reported with anti-BCMA BsAbs use.

### GPRC5D- specific toxicity

GPRC5D antigen is highly expressed on plasma cells. It is also expressed on cortical cells of the hair shaft, and the central region of the filiform papillae of the tongue and salivary glands. Low levels of GPRC5D mRNA have been detected in the motor neurons of the inferior olivary nucleus of the brain stem. Talquetamab administration is associated with early-onset severe loss of

taste, dry mouth, rashes, dry skin, and nail changes. Hair changes consisting of loss of eye lashes or eyebrows are seen less [3].

## BsAbs combinations and its efficacy

Combinations of BsAb with other BsAb or other anti-myeloma agents have been tested in several trials. Major trials are.

- Testing teclistamab in various combinations e.g. a combination of daratumumab and lenalidomide in the relapsed refractory setting (Phase 1b MajesTEC -2 trial).
- Comparative study of a teclistamab-daratumumab-lenalidomide combination versus. daratumumab-lenalidomide-dexamethasone combination in NDMM patients ineligible or not intended for autologous stem cell transplant as initial treatment (phase 3 MajesTEC -7 study, NCT05552222).
- Study the combination of s.c. talquetamab and daratumumab in RRMM (the TRIMM-2 trial).
- Testing addition of pomalidomide to talquetamab (the Phase 1b MonumenTAL -2 trial).
- Testing simultaneous combination of anti BCMA-teclistamab and anti GPRC5D- talquetamab targeted BsAbs to overcome resistance mechanisms by targeting two myeloma antigens (the Phase 1b RedirecTT-1 trial). Dual BsAbs targeting still not overcome the high risk extramedullary disease (NCT04586426) [2].
- Talquetamab BsAbs and PD-L1 checkpoint inhibitors combination can enhance the cytotoxic properties of NK and T cells against myeloma cells in R/R patients (The TRIMM-3 phase 1 study, NCT05338775).
- BsAbs plus cereblon E3 ligase modulatory drugs (CELMoDs): CELMoDs could enhance the clinical activity of BsAbs and could potentially mitigate the CRS induced by BsAbs by inhibiting proinflammatory cytokines secretion.
- Anti-BCMA- teclistamab and gamma-secretase inhibitors (nirogacestat) combination was evaluated in heavily pretreated patients (median of four prior lines of therapy, triple-class refractory=71%). Gamma-secretase inhibitors enhance the efficacy of anti-BCMA BsAbs by reducing soluble BCMA levels and increase BCMA expression in plasma cells (MajesTEC-2 trial) [5].

## Advantages and disadvantages of BsAbs over CAR-T cell therapy

CAR-T cell therapy have superior efficacy over BsAbs. However, the frequency and severity of CRS and neurological toxicity are higher with CAR-T cell therapy compared to BsAbs therapy. The potential for fatal complications such as immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome remain problematic. Idiosyncratic CAR-T toxicities also exist. Delayed onset of cranial nerve palsies, and neurocognitive

adverse events (micrographia, tremors, inattention, psychomotor retardation) affect 5-10% of MM patients. In addition, CAR-T use is hindered by manufacturing constraints. BsAbs is an immediate, 'off the-shelf' highly effective therapy, filling a critical niche for rapidly progressive relapsed patients. In comparison, the time needed for commercial CAR-T manufacture range from 4-8 weeks [5].

## Optimal sequencing of BsAbs

CAR-T cell therapy is the most effective primary cellular therapy of MM, while BsAbs is an effective post-CAR-T salvage therapy. Possible explanations for the diminished efficacy of CAR-T cell following BsAbs therapy include antigen escape and T-cell exhaustion. Salvage with BsAbs (both BCMA- and GPRC5D-directed) or CAR T was found to be superior to conventional doublet, triplet, or quadruplet chemotherapeutic combinations in relapsed MM patients [5].

## Future directions

The optimal patient population, schedule and duration of BsAbs therapy is the subject of active investigation. Currently, BsAbs are administered continuously until disease progression or intolerance. T-cell exhaustion induced by their ongoing stimulation is one of the mechanisms of resistance to T-cell-directed therapies. Treatment-free intervals and extended dosing schedules, a combination of BsAbs and immune checkpoint inhibitors, generation of trispecific antibodies that target PD-L1, and concurrent treatment with low-dose cyclophosphamide, which improves effector T-cell function by depleting regulatory T-cells are all strategies explored to overcome T-cell exhaustion [5].

## Conclusion

The myeloma treatment landscape is expected to change in the near future. These novel immunotherapies may be introduced in early relapse and in NDMM with the goals of achieving deeper responses in limited duration of therapy and providing the potential for cure. However, the ideal sequence, combination, and duration of use of these novel therapies and how to best incorporate these agents with the current myeloma landscape will be the subject of multiple trials. Novel plasma cell surface targets will continue to be developed.

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DOI: [10.19080/CTOIJ.2025.28.556231](https://doi.org/10.19080/CTOIJ.2025.28.556231)

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