# Current use of bispecific antibodies to treat multiple myeloma

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**Targeted immunotherapy has significantly improved the outcome of patients with hematological malignancies by leveraging the power of the immune system to eliminate tumor cells. In multiple myeloma (MM), bispecific T-cell engagers (BsAb) targeting B-cell maturation antigen (BCMA), G protein–coupled receptor, class C, group 5, member D (GPRC5D), and Fc receptor-like 5 (FcRL5) have already demonstrated remarkable clinical activity in triple-class refractory patients. However, responses to BsAb are not universal, and resistance often emerges while on therapy. Mechanisms mediating resistance are tumor intrinsic or immune dependent. Reported tumor intrinsic factors include antigenic loss (biallelic or functional) through deletions or mutations of target genes, increased soluble BCMA (for BCMA targeting BsAb), high tumor burden, and extramedullary disease. Immune-mediated resistance are largely dependent on T-cell fitness and tolerant immune environment. Understanding these mechanisms will allow the design of optimized BsAb therapy and an informed approach to sequencing and combining these molecules with other anti-MM agents and immune therapies.**

**LEARNING OBJECTIVES**

- Current use, efficacy, and sequencing of bispecific antibodies in multiple myeloma
- Understanding the mechanisms of action and escape to bispecific antibodies in multiple myeloma

## CLINICAL CASE

A 76-year-old female with Revised International Staging System (R-ISS) stage III multiple myeloma (MM) has disease relapse following four lines of therapy, including cyclophosphamide, bortezomib, and dexamethasone (first line), daratumumab, lenalidomide, and dexamethasone (second line), pomalidomide and dexamethasone (third line), and carfilzomib and dexamethasone (fourth line). This patient with penta-refractory MM enrolls in a clinical trial and receives anti-BCMA bispecific antibody as her fifth line of therapy. She attains complete remission with a duration of response of 12 months, after which she has a recurrence of her disease.

## Introduction

The advent of T-cell redirecting immunotherapies such as chimeric antigen receptor T cells (CAR T) and bispecific antibodies (BsAb) has revolutionized the treatment of multiple myeloma (MM). While these therapies have demonstrated promising results in inducing deep remissions in patients with relapsed refractory MM, universal disease responses remains a challenge and relapses invariably occur. Clinical trials of single-agent CAR T or BsAb targeting MM-specific antigen in heavily pretreated patients resulted in high responses with variable duration of remission lasting from a few months to over two years.[1-8] Given the increasing number of CAR T and BsAb agents at various stages of clinical development in MM, there is a pressing need to integrate biological correlates and clinical parameters to generate predictive markers that can guide the selection of therapy sequences and optimal combinatorial strategies for individual patients. This article focuses on the current use of BsAb in MM, reviewing the pre-clinical and clinical studies that support data-driven clinical decisions in the rapidly advancing era of immunotherapy.

## Mechanism of action of BsAb

T-cell–engaging BsAb are synthetic molecules that facilitate the interaction between effector T cells and target cells, promoting the eradication of tumors through T-cell–mediated cytotoxicity. By inducing target and effector cells proximity, BsAb support the formation of cytolytic immunologic synapses. This leads to the release of

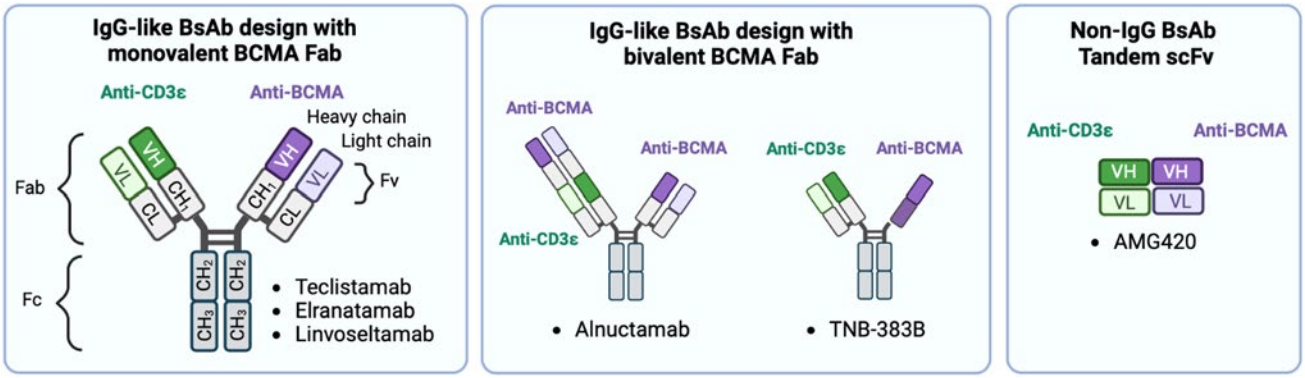


**Figure 1. Structure of anti-BCMA bispecific antibodies.** Anti-BCMA BsAb can be classified into immunoglobulin G (IgG)-like and non-IgG-like based on their structures. IgG-like BsAb consist of antibody binding fragments (Fab) which recognize target antigens, and a crystallizable fragment (Fc). In addition to having one Fab targeting CD3 (anti-CD3ε), BsAb with monovalent BCMA Fab consists of one Fab targeting BCMA (anti-BCMA). BsAb with bivalent BCMA Fabs are designed with either two anti-BCMA Fabs or two anti-BCMA variable domain of heavy chains (VH). Non-IgG BsAb, AMG420, is synthesized as tandem single chain Fvs and lacks Fc. CH, constant domain of heavy chain; CL, constant domain of light chain; Fv, variable fragment; VL, variable domain of light chain.

cytotoxic effectors such as perforin and granzyme B from the activated T cells, triggering tumor cell apoptosis and pyroptosis. In contrast to canonical T-cell activation, which requires T-cell receptor (TCR) recognition of a peptide bound to major histocompatibility complex (MHC) (signal 1) and co-stimulation (signal 2), BsAb mediate both TCR and co-stimulation independent polyclonal T-cell activation.

BsAb exert their therapeutic effect based on their unique structural design, which includes variations in epitope specificities and affinities, IgG subclasses, Fc modifications, and Fab valency, among others. While over 100 different BsAb forms are developed, they can be broadly categorized into IgG-like and non–IgG-like formats, based on the presence or absence of the fragment crystallizable domain (Fc). Currently, all the BsAb in active clinical development for MM have IgG-like structures, with one Fab targeting CD3 on T cells and the other targeting the MM cell surface antigen, such as BCMA (Figure 1). The most advanced anti-BCMA BsAb in clinical development for MM, teclistamab, elranatamab, and linvoseltamab, have monovalent anti-BCMA Fab, while alnuctamab and ABBV-383 contain bivalent BCMA binding fragments. In contrast, the anti-BCMA BsAb AMG420, initially developed as a non–IgG-like format in a tandem single-chain variable fragment (scFv) lacking Fc region, had reduced serum half-life, which necessitated frequent administration schedules. Consequently, the development of AMG420 and its variations have been discontinued.[9]

The therapeutic activity of BsAb relies on the expression of target antigens on the surface of MM cells. BCMA, a type III transmembrane protein, is highly expressed on malignant plasma cells and promotes prosurvival signals upon ligand binding. Other targets for T-cell immunotherapy development with BsAb include G protein–coupled receptor, class C, group 5 (GPRC5D), fragment crystallizable receptor-like 5 (FcRL5, also referred to as FcRH5), and CD38.[10] While CD3-expressing T cells are the primary targets for effector cell engagement, several preclinical studies are currently assessing the tumoricidal efficacy of BsAb that bind to CD16A, NKp30, NKG2D, or MICA for recruiting innate immune effectors such as NK cells. A summary of the BsAb currently in clinical development is provided in Table 1.

## Current use of bispecific antibodies

Until recently, patients with triple-class- or penta-refractory MM had limited options for salvage therapy, leading to poor clinical outcomes with median overall survival rates of less than 12 months and 6 months, respectively.[11] The introduction of T-cell–based anti-MM immunotherapies into clinical practice was highly anticipated with the prospect that therapeutically reinstating the host anti-cancer immunity could induce deep remissions in patients with end-stage myeloma.

Teclistamab is the first anti-BCMA BsAb that has been approved by regulatory agencies for the treatment of patients with MM who have received 4 or more lines of therapies including proteasome inhibitor (PI), immunomodulatory agent (IMiD), and anti-CD38 monoclonal antibody. The multicenter phase 1/2 MajesTEC-1 trial, which included 165 patients, including 77% and 30% of triple-class and penta-refractory patients, respectively, demonstrated that single-agent weekly administration of teclistamab (1.5 mg/kg) generated an overall response rate (ORR) of 63.0%. At a median follow-up of 14.1 months, the median duration of response was 18.4 months, with a median progression-free survival (PFS) of 11.3 months.[2] Subgroup analysis of MajesTEC-1 revealed that patients with high-risk disease features, including R-ISS stage III, extramedullary plasmacytoma, and increased bone marrow plasma cell burden ≥60%, tended to have lower response rates compared with those with standard-risk MM.[2,12] Of interest, while advanced-stage ISS is traditionally associated with poor outcome with standard myeloma therapeutics, the response rates of patients with high-risk cytogenetics was comparable to those with standard-risk cytogenetic profiles.[2] Albeit small patient numbers, the data suggest that traditional tumor cytogenetic risk profiles may have a less important role in stratifying patient response to BsAb therapies.

In the ongoing phase 1 MagnetisMM-1 study of elranatamab,[13] among 55 patients (91% triple-class refractory) at a median follow-up of 12 months, ORR was 64%, with 38% achieving ≥ complete response. Importantly, this trial included 13 patients with prior BCMA therapies, including antibody drug conjugate, CAR T, or both. Within this subgroup, overall response rate was 54% (7/13), with 6 patients achieving ≥ very good partial

**Table 1. T-cell–engaging bispecific antibodies in clinical development**

| Bispecific antibody | Target | Format | Valency | Route of administration | Properties |
|---|---|---|---|---|---|
| Teclistamab (JNJ-640079957) | BCMA × CD3 | IgG4 duobody | Monovalent CD3 binding<br>Monovalent BCMA binding | Subcutaneous | Fc mutated ↑ half-life, and ↓ immunologic effector function–mediating CRS |
| Elranatamab (PF-06863135) | BCMA × CD3 | IgG2a BsAb | Monovalent CD3 binding<br>Monovalent BCMA binding | Subcutaneous | Fc mutated ↑ half-life, heterodimerization, and ↓ immunologic effector function–mediating CRS |
| TNB-383B (ABBV-383) | BCMA × CD3 | IgG4 BsAb | Low-affinity CD3 binding<br>Bivalent BCMA binding | Intravenous | Decouples T-cell activation from CRS and activates Teff over Tregs |
| Linvoseltamab (REGN5458) | BCMA × CD3 | IgG4 BsAb | Monovalent CD3 binding<br>Monovalent BCMA binding | Intravenous | Fully human, VelociBi™ Fc silent region, mutation in protein A binding site |
| Alnuctamab (CC-93269) | BCMA × CD3 | IgG1 BsAb, asymmetrical 2 + 1 format | Monovalent CD3 binding<br>Bivalent BCMA binding | Intravenous/ subcutaneous | Heterodimeric mutated Fc with intact FcRn, and ↓ immunologic effector function–mediating CRS |
| Talquetamab (JNJ-64407564) | GPRC5D × CD3 | IgG4 duobody | Monovalent CD3 binding<br>Monovalent GPRC5D binding | Subcutaneous | Fc-mutated ↑ half-life, and ↓ immunologic effector function–mediating CRS |
| Forimtamig RG6234 (RO7425781) | GPRC5D × CD3 | IgG1, asymmetrical 2 + 1 format | Monovlent CD3 binding<br>Bivalent GPRC5D binding | Intravenous/ subcutaneous | Fc-mutated (silent Fc) ↑ half-life |
| Cevostamab (BFCR4350A) | FcRL5 × CD3 | Humanized IgG1-based Ab | Monovalent CD3 binding<br>Monovalent FcRL5 binding | Intravenous | FcRL5 expressed on B and plasma cells |

BCMA, B-cell maturation antigen; CD3, cluster of differentiation 3; CRS, cytokine release syndrome; FcRL5, fragment crystallizable receptor-like 5 (FcRL5) also referred to as FcRH5; GPRC5D, G protein–coupled receptor, class C, group 5.

response. Similarly, in the MagnetisMM-3 phase 2 study cohort of BCMA-naïve patients (N = 123), ORR was 61%. Predictors of poor response included ISS stage III disease and the presence of extramedullary disease. At a median follow-up of 10.4 months, median PFS and overall survival were not reached.[5]

The MonumenTAL-1 trial examined the safety and efficacy of talquetamab, an anti-GPRC5D BsAb in patients with a median of 6 prior lines of therapy.[4] At the active subcutaneous and intravenous doses, 68% and 72% of patients responded, respectively. At 11.7- and 4.2-month follow-up for the 405 µg/kg and 800 µg/kg doses, the response was 10.2 months and 7.8 months, respectively. Responses were seen in 55.6% to 66.7% of patients with high-risk cytogenetics, 40% to 45% of patients with extramedullary disease, and 50% of patients previously treated with anti-BCMA CAR T or BsAb.[4]

In addition to the aforementioned BsAbs listed, other BCMA (linvoseltamab, alnuctamab, ABBV-383) and non-BCMA targeting BsAb (cevostamab, forimtamig) have reported similar efficacy in advanced MM.[7,8,14-16] As clinical trials continue to provide encouraging updates on the efficacy of single-agent BsAb in inducing deep remission in heavily pretreated MM patients, important questions remain regarding the optimal duration of therapy (fixed vs. continuous schedules), sequencing of BsAbs and CAR T, and combinations with other anti-MM backbone therapies (summarized in Table 2). Of note, while BsAbs have similar reported activity in early-phase 1/2 trials, they do differ based on their target, valency, affinity, and structural design (Table 1). These differences may have therapeutic relevance, as discussed further below. Emerging data regarding the sequencing of BsAb with adoptive cellular therapies support sustained efficacy of BsAb post CAR T therapy (CAR T → BsAb), while the reverse sequence (BsAb → CAR T) significantly reduces the PFS of CAR T recipients.[4,5,8,17-19]

## Resistance to bispecific antibody therapies

Resistance to BsAb therapy in MM can occur through various mechanisms, which can be broadly classified into two categories: (1) immune dysfunction (T cell or immune microenvironment) and (2) tumor-intrinsic adaptation (antigenic drifting and disease burden). A summary of these mechanisms are illustrated in Figure 2. Understanding the interplay among these mechanisms and developing strategies to overcome them are critical to improving the efficacy of BsAb.

## Immune-related factors

### T-cell dysfunction

The efficacy of BsAb therapy depends on the fitness of the immune effector cells. MM is characterized by progressive T-cell dysfunction. Marrow-infiltrating lymphocytes (MIL) in MM consist of heterogeneous T-cell populations that undergo exhaustion characterized by terminal differentiation, loss of effector functions, and expression of inhibitory receptors from suboptimal priming and chronic antigen stimulation in the immunosuppressive tumor microenvironment.[20-24] Functional and numerical defects in T cells not only promote MM disease progression but also portend poor response to BsAb therapy. Correlative studies from the MajesTEC-1 trial presented at ASH 2022 suggested

**Table 2. Selected clinical trials of bispecific antibodies in multiple myeloma**

| Trial | Patient | Intervention | Phase |
|---|---|---|---|
| **MajesTEC-4 (NCT05243797)** | NDMM | Post-autologous stem cell transplant:<br>TEC + Len<br>vs.<br>Len<br>vs.<br>TEC | Phase 3 |
| **MajesTEC-5 (NCT05695508)** | NDMM transplant eligible | Induction with:<br>TEC + Dara + Len + dex<br>vs.<br>TEC + Bort + Len + Dara + dex<br>vs.<br>Standard of care<br><br>Followed by:<br>TEC + Dara + Len maintenance | Phase 2 |
| **MajesTEC-7 (NCT05552222)** | NDMM transplant noneligible | TEC + Dara + Len<br>vs.<br>Dara + Len + dex | Phase 3 |
| **MagnetisMM-7 (NCT05317416)** | NDMM | Post-autologous stem cell transplant:<br>ELRA<br>vs.<br>Len | Phase 3 |
| **MajesTEC-2 (NCT04722146)** | NDMM and RRMM | TEC + Dara + Pom<br>vs.<br>TEC + Dara + Pom + Bort<br>(21- or 28-day cycle)<br>vs.<br>TEC + nirogacestat<br>vs.<br>TEC + Len<br>vs.<br>TEC + Dara + Len | Phase 1b |
| **MajesTEC-3 (NCT05083169)** | RRMM, 1–3 prior lines including PI and Len | TEC + Dara<br>vs.<br>Dara + Pom + dex<br>or Dara + Bort + dex | Phase 3 |
| **MajesTEC-9 (NCT05572515)** | RRMM, 1–3 prior lines including anti-CD38 and IMiD | TEC<br>vs.<br>Pom + Bort + dex<br>or Carf + dex | Phase 3 |
| **MagnetisMM-6 (NCT05623020)** | Part 1: RRMM 1–2 prior lines of therapy including IMiD and PI<br>or<br>NDMM transplant noneligible<br>Part 2: NDMM transplant noneligible | ELRA + Dara + Len<br>vs.<br>Dara + Len + dex | Phase 3 |
| **MagnetisMM-1 (NCT03269136)** | RRMM, triple-class refractory | ELRA<br>vs.<br>ELRA + dex<br>vs.<br>ELRA + Len<br>vs.<br>ELRA + Pom | Phase 1 |
| **MagnetisMM-3 (NCT04649359)** | RRMM, triple-class refractory<br>Cohort A: no prior anti-BCMA<br>Cohort B: prior anti-BCMA ADC or CAR T | ELRA | Phase 2 |
| **MagnetisMM-4 (NCT05090566)** | RRMM, triple-class refractory | ELRA + nirogacestat<br>vs.<br>ELRA + Len + dex | Phase 1b/2 |
| **MagnetisMM-5 (NCT05020236)** | RRMM, prior therapy including IMiD and PI | ELRA<br>vs.<br>ELRA + Dara<br>vs.<br>Dara + Pom + dex | Phase 3 |

**Table 2. Selected clinical trials of bispecific antibodies in multiple myeloma (*Continued*)**

| Trial | Patient | Intervention | Phase |
|---|---|---|---|
| **TRIMM-2 (NCT04108195)** | RRMM, 3 prior lines including PI and IMiD | TEC + Dara<br>vs.<br>TALQ_+ Dara<br>vs.<br>TEC + Dara + Pom<br>vs.<br>TALQ_+ Dara + Pom | Phase 1b |
| **RedirecTT-1 (NCT04586426)** | RRMM | TALQ_+ TEC + Dara | Phase 1b |
| **TRIMM-3 (NCT05338775)** | RRMM | TALQ_+ TEC + PD-1 inhibitor | Phase 1b |
| **MonumenTAL-2 (NCT05050097)** | NDMM | TALQ_+ Carf<br>vs.<br>TALQ_+ Dara + Carf<br>vs.<br>TALQ_+ Len<br>vs.<br>TALQ_+ Dara + Len<br>vs.<br>TALQ_+ Pom | Phase 1b |
| **MonumenTAL-3 (NCT05455320)** | RRMM | TALQ_+ Dara + Pom<br>vs.<br>Dara + Pom + dex<br>vs.<br>TALQ_+ Dara + dex | Phase 3 |
| **IFM 2021–01 (NCT05572229)** | Older adults, age ≥65 | TEC + Dara<br>vs.<br>TEC + Len | Phase 2 |
| **Immuno-PRISM (NCT05469893)** | High-risk SMM | Len/dex<br>vs.<br>TEC | Phase 2 |

ADC, antibody drug conjugate; Bort, bortezomib; Carf, carfilzomib; Dara, daratumumab; dex, dexamethasone; ELRA, elranatamab; IMiD, immunomodulatory drug; Len, lenalidomide; NDMM, newly diagnosed multiple myeloma; PI, proteasome inhibitor; Pom, pomalidomide; RRMM, relapsed refractory multiple myeloma; SMM, smouldering multiple myeloma; TALQ_, talquetamab; TEC, teclistamab.

that a higher number of baseline peripheral T cells, increased frequency of naïve CD8 T cells (CD45RA+ CD27+), and lower regulatory T cells (Treg) were seen in the peripheral blood of responding patients than in nonresponders. Clinical response to teclistamab was also associated with lower-expression inhibitory receptors (PD-1, TIM3, and CD38) on T cells.[12] A comprehensive single-cell interrogation of marrow and peripheral blood T cells demonstrated that increased frequency of exhausted CD8+ TOX+T cells is associated with response failure while clonal expansion of fit preexisting T cells is found in patients with clinical response.[25] In this study, CXCR3-positive CD8 cells are demonstrated to be the main mediators of BsAb cytotoxicity. Furthermore, serial interrogation of the TCR repertoire from patients who respond to anti-BCMA BsAb suggest that the expansion and persistence of putatively tumor-reactive TCR clonotypes between the pre- versus post-therapy timepoints is associated with therapy response while such clonotypic persistence is lacking in nonresponders. BsAb, in effect, induce the pooling of peripheral blood T cells to the bone marrow–tumor microenvironment and enable the selective expansion of tumor-reactive clonotypic CD8+ T cells.[26] A preexisting global exhausted T-cell profile, in both the peripheral blood and bone marrow compartments, is therefore an impediment to effective BsAb response. In addition to preexisting T-cell exhaustion observed in MM patients prior to the initiation of BsAb therapy, repetitive T-cell engagement with BsAb administration may further exacerbate T-cell dysfunction[27]; integrating treatment-free interval into the therapy regimen may mitigate this effect, allowing for a more durable therapeutic benefit while attenuating treatment-emergent adverse events.[27]

### Immunosuppressive bone marrow microenvironment

Malignant plasma cells in MM are in complex interplay with the bone marrow accessory cells within the tumor microenvironment, which together promote MM cell survival and growth while suppressing effective anti-tumor immune activity. The bone marrow microenvironment is characterized by the presence of stromal cells, osteoclasts, myeloid-derived suppressor cells, tumor-associated macrophages, plasmacytoid dendritic cells, and regulatory T or B cells.[28] These cells, in combination with the secretion of immunosuppressive cytokines, including IL-6, IL-8, IL-10, IL-15, IL-18, and VEGF, and the expression of inhibitors such as soluble MICA, TGF-β, and indoleamine 2,3-dioxygenase, impair effective T-cell responses.[21,29] The success of BsAb therapy relies on recruiting T cells into this immunosuppressive milieu, where they must overcome multiple mechanisms that hinder T-cell metabolism and counter their activation, expansion, and persistence.

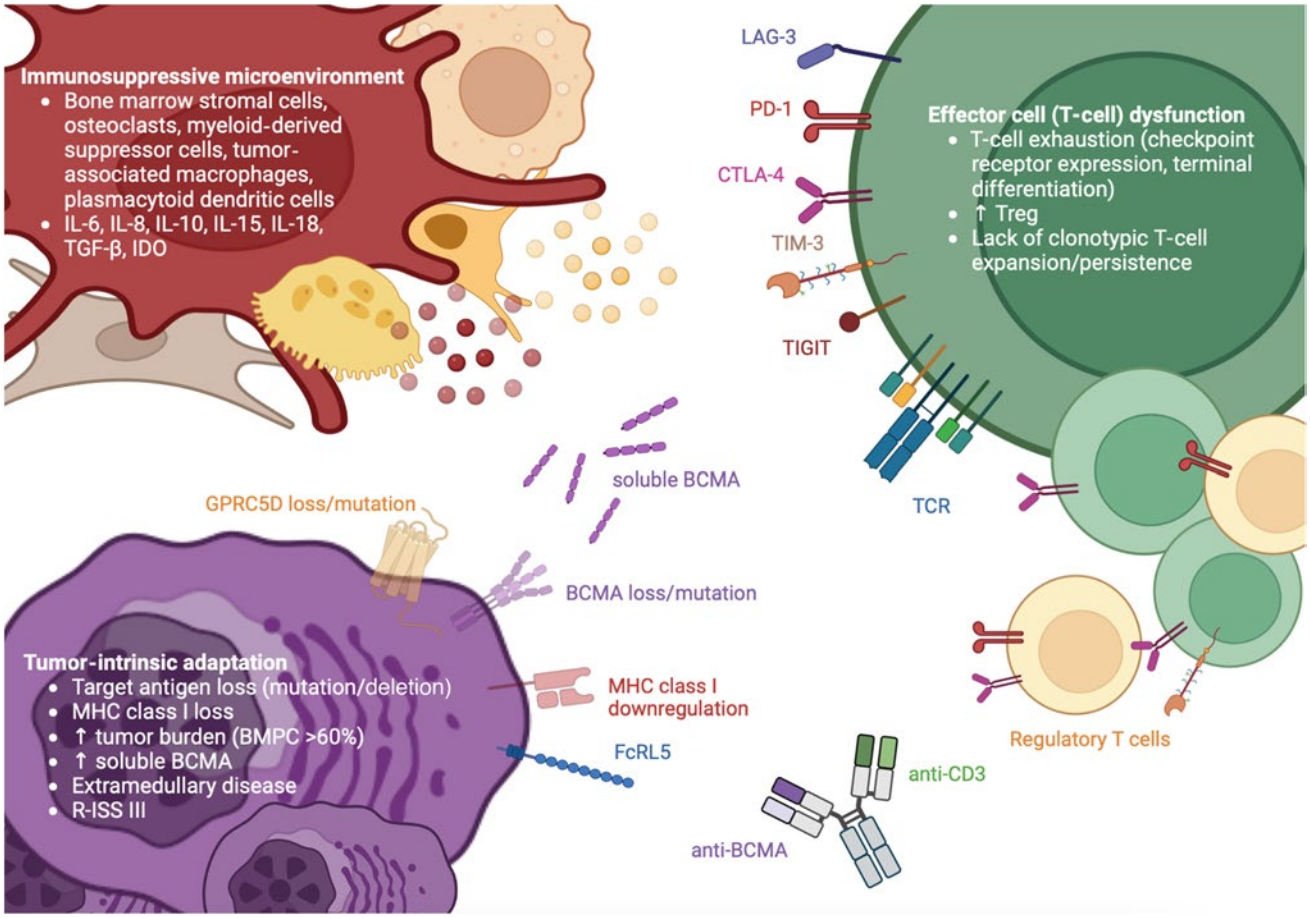


**Figure 2. Mechanisms of resistance to bispecific antibodies in multiple myeloma.** Immunosuppressive tumor microenvironment, reduced T cell fitness, and tumor-intrinsic mechanisms can contribute to multiple myeloma resistance to BsAb. BMPC, bone marrow plasma cells; CTLA-4, cytotoxic T-lymphocyte associated protein 4; LAG-3, lymphocyte activation gene-3; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; TCR, T cell receptor; TIGIT, T cell immunoreceptor with Ig and ITIM domains; TIM-3, T cell immunoglobulin domain and mucin domain-3; Treg, regulatory T cells.

The immunomodulatory effect of anti-MM agents, including immunomodulatory drugs (IMiD)[30] and daratumumab,[31] may further potentiate BsAb activity, and these combinations are actively being investigated in clinical trials (refer to Table 2).

## Tumor-related factors

### Antigenic loss

While bispecific antibodies effectively eradicate the bulk of a tumor by targeting ubiquitously expressed surface antigens, such therapeutically enhanced anti-cancer immunity exerts clonal evolutionary selective pressures. This can facilitate the emergence of clones whose growth is fueled by compensatory mechanisms that allow immune evasion and convergent evolution, ultimately leading to clinical relapse. One of the key mechanisms of tumor-intrinsic adaptive resistance to targeted immunotherapies is antigen escape. Loss of BCMA expression post anti-BCMA CAR T is detected in around 4% of cases, while preexisting heterozygous deletions of *TNFRSF17* (gene encoding BCMA) is found in up to 4% of the immunotherapy-naïve MM patient population.[1,32] To date, there are 3 published reports of BCMA-negative MM relapse post anti-BCMA CAR T and two cases post anti-BCMA BsAb.[32-36] In these reports, BCMA antigen loss occurred through biallelic deletion at the *TNFRSF17* gene locus or monoallelic deletion coupled with a truncating nonsense mutation in the remaining *TNFRSF17* allele. In addition to biallelic deletions at the *TNFRSF17* gene locus, single amino acid mutations or deletions in the extracellular domain of BCMA were recently shown to confer resistance to some anti-BCMA BsAb.[36] Deletions or mutations on *TNFRSF17* were identified in 6 of 14 patients who progressed post anti-BCMA BsAb. Importantly, in this preclinical study, alternative BsAb design (asymmetrical bivalent anti-BCMA binding domains) or anti-BCMA CAR T overcame monovalent anti-BCMA BsAb resistance resulting from BCMA extracellular domain mutations.[36] Hence, resistance to one anti-BCMA BsAb may not preclude re-treatment with other BCMA-targeting agents.

GPRC5D loss or reduction of surface antigen expression was detected in all 6 of 6 patients who progressed post anti-GPRC5D CAR T.[3] Four additional cases of MM relapse with biallelic genomic events on *GPRC5D* (biallelic deletions or monoallelic deletion and mutations) post anti-GPRC5D BsAb have also been reported.[36] Of note, up to 15% of T-cell immunotherapy-naïve patients have preexisting heterozygous loss of *GPRC5D*.[32] Altogether, BCMA and GPRC5D antigen biallelic or functional loss are

important mechanisms of resistance to BsAb in MM. Such findings support the ongoing development of alternative or multiple antigen-targeting therapeutic approaches as well as optimizing the design of BsAb agents to better target antigen escape clones. Clinical trials are also underway to combine two BsAb that target BCMA and GPRC5D (NCT04586426, NCT05338775).

### Soluble BCMA and myeloma disease burden

Clinical trials have shown that high disease burden, defined as ≥60% bone marrow plasma cells, is associated with primary refractoriness to single-agent anti-BCMA or anti-GPRC5D BsAb in patients with RRMM.[2,4] Along with bone marrow plasma cell assessment, measuring soluble BCMA (sBCMA) levels is an important correlate for evaluating disease burden and predicting BsAb therapy response. High sBCMA levels have been associated with lower response rates to single-agent teclistamab and were correlated with high R-ISS stage, increased bone marrow plasma cells (>60%), and the presence of extramedullary disease.[12] This observation raises several questions about the underlying mechanisms that drive the reduced efficacy of BsAb in the setting of elevated sBCMA levels. Does the lack of response reflect poor penetration and limited T-cell trafficking and engagement in the tumor bulk, as seen in the relatively ineffective response to BsAb in solid tumors?[37] Alternatively, could sBCMA serve as a ligand sink that traps anti-BCMA BsAb in serum, preventing their binding to MM cells' surface BCMA molecules?[12,38] Moreover, elevated sBCMA may result from a tumor-intrinsic evasion mechanism by which the MM cells enhance gamma secretase activity to downregulate surface BCMA expression. These mechanisms can be amenable to targeting by gamma secretase inhibitors,[39] and this is being tested in ongoing clinical trials (NCT04722146).

Debulking MM with cytotoxic agents prior to or in combination with BsAb therapy may help restore BsAb-mediated cytotoxicity in high disease burden settings.[40] Furthermore, the combination of novel cereblon E3 ligase modulator (CELMoD) such as mezigdomide[41] has been shown to sensitize MM cells to alnuctamab-mediated cytotoxicity, in part through the induction of DNAM-1 ligands on MM cell surface.[42] Ongoing studies of BsAb in combination with other anti-MM agents will provide valuable insight into whether combination therapy can overcome the current limitations of BsAb therapy in the setting of high disease burden.

## CLINICAL CASE (continued)

Whole genome sequencing of the CD138+ sorted MM cells at relapse demonstrated that the patient had a newly detectable clonal mutation in *TNFRSF17* [p. Arg27Pro] coupled with a monoallelic loss of *TNFRSF17* gene locus. This immune-selected mutant clone completely abrogated BCMA affinity of the BsAb Fab moiety with which it was treated.[36] Subsequent immediate treatment with another BsAb targeting GPRC5D resulted in an ongoing molecular remission at 1 year of follow-up.

## Conclusion

The rapid progress in the development of BsAb and other T-cell immunotherapies for MM is revolutionary. However, the adaptive nature of MM tumor cells and their ability to evade the immune system necessitates an ongoing parallel effort in both clinical and preclinical research. It is crucial to investigate the mechanisms of resistance to these therapies and develop innovative therapeutic strategies to overcome them. Moreover, identifying predictive biomarkers of response to BsAb will enable the deployment of personalized immune-therapy.

### Conflict-of-interest disclosure

Holly Lee: no competing financial interests to declare.
Paola Neri: received speaker's bureau honoraria from BMS, Janssen, and Sanofi and is a consultant/advisory board member for BMS and Janssen.
Nizar J. Bahlis: has received research funding from Pfizer, and received speaker's bureau honoraria from Amgen, BMS, Sanofi, Pfizer, and Janssen and is a consultant/advisory board member for BMS, Janssen, and Pfizer.

### Off-label drug use

Holly Lee: There are no off-label drug uses to disclose.
Paola Neri: There are no off-label drug uses to disclose.
Nizar J. Bahlis: There are no off-label drug uses to disclose.

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