


T-Cell Engagers In Multiple Myeloma: A Clinical Review

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Abstract: T-cell engagers (TCEs) are engineered to bind both the CD3 subunit on T-cells and specific antigens on tumor cells, triggering T-cell activation and tumor cell lysis. TCEs targeting B-cell maturation antigen (BCMA) and G-protein-coupled receptor, class C, group 5, member D (GPCR5D) have demonstrated significant clinical activity in heavily pretreated patients with relapsed/refractory multiple myeloma (RRMM). As a monotherapy, TCEs have had overall response rates (ORRs) of over 60%, with deep and durable hematological responses. Common toxicities include cytokine release syndrome (CRS), infections, and on-target off-tumor effects. Ongoing research looks to enhance the efficacy and tolerability of TCEs for the next generation of products to play an even bigger role in treating patients with MM.

Keywords: T-cell engagers, multiple myeloma, BCMA, GPCR5D

Introduction

Multiple myeloma (MM) is a clonal plasma cell neoplasm predominantly originating within the bone marrow, leading to several clinical complications, including osteolytic bone lesions, anemia, renal insufficiency, and immunodeficiency.¹ Over the past two decades, survival rates for individuals with MM have markedly improved.^{2,3} This progress can be attributed to the introduction of novel therapeutic agents such as proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies, as well as advancements in autologous stem cell transplantation.¹ Despite advancements in therapeutic approaches, MM remains a mostly incurable disease, with most patients experiencing multiple relapses with eventual resistance to most conventional anti-MM therapies. Recent advances in understanding the immune effector system have led to its exploitation as a crucial tool in cancer treatment, selectively targeting and eliminating cancer cells. This approach has opened new treatment possibilities in MM, with promising strategies like T-cell engagers (TCEs) and chimeric antigen receptor (CAR) - T cell therapies. TCEs are antibodies engineered to engage two distinct antigens simultaneously, one targeting a specific antigen highly expressed on the cell membrane of cancer cells and the other on T-cells.⁴ Conversely, CAR-T cell therapies involve genetically modifying a patient's T-cells to express receptors that selectively identify and bind to specific antigens on cancer cells.⁵

Modern TCE technologies have evolved significantly to optimize these therapeutics' efficacy, specificity, and safety through improved engineering techniques. For example, orthogonal Fab interfaces refine antigen specificity by modifying variable antibody regions, reducing cross-reactivity, and ensuring accurate binding to target antigens.⁶⁻⁸ Another advancement is the DuoBody platform, which creates TCEs through controlled heavy and light chain exchanges, providing stability and functionality.⁹

Further technological progress includes XmAb engineering, which enhances Fc domain functionality to boost immune effector responses like antibody-dependent cellular cytotoxicity (ADCC) while extending the therapeutic half-life.^{10,11} CrossMab technology simplifies the production of bispecific antibodies by rearranging light and heavy chains to maintain binding specificity and scalability.¹² Additionally, the knobs-into-holes design enhances bispecific antibody assembly by promoting precise heterodimer formation, improving pharmacokinetics and overall therapeutic

effectiveness.¹³ These innovations have significantly enhanced the safety, scalability, and clinical efficacy of TCEs, enabling their integration into cancer treatment paradigms.¹⁴

This review will explore the clinical application of FDA-approved TCEs in treating MM. We will discuss their mechanism of action, clinical efficacy, toxicities, and the challenges and future directions in this rapidly evolving field.

Mechanism of Action

Native IgG immunoglobulins have two heavy and light chains (kappa or lambda).¹⁵ They have an Fc portion, responsible for complement activation and immune cell engagement, and a Fab portion, which binds to antigens with its variable regions. Normal antibodies are bivalent and monospecific, meaning both Fab segments have the same antigen specificity. The Fc portion also influences the antibody's half-life by preventing rapid renal clearance and interacting with neonatal receptors to regulate IgG levels.¹⁵ Engineered, therapeutic monoclonal antibodies target specific antigens on tumor cells to direct immune processes, like antibody-dependent cytotoxicity (ADC), to destroy cells expressing the target antigen. In contrast, bispecific antibodies are more complex than natural or engineered antibodies.¹⁶ Unlike natural antibodies, bispecific antibodies such as the TCEs must bind immune cells monovalently to avoid T-cell crosslinking.¹⁷ They also avoid triggering immunogenicity and the formation of anti-drug antibodies by containing chimeric, humanized, or fully human antibodies. Thus, TCEs tend to have high-affinity domains to bind specific antigens on tumor cells and a single lower-affinity domain to bind immune cells, usually CD3 on T-cells. This binding forms an immunologic synapse, activating the T-cell receptor and leading to the lysis of the target cancer cell. TCEs induce dose-dependent T-cell activation, primarily of CD8+ cells, which is marked via the expression of activation markers such as CD69 and CD25. The release of lytic enzymes, such as granzyme B and perforin, disrupts tumor cell membranes, leading to tumor cell apoptosis.¹⁸ This is followed by further T-cell proliferation, trafficking to the tumor microenvironment, and dose-dependent tumor cell lysis.^{18–20} Thus, unlike the usual immune responses that require interaction with the major histocompatibility complex (MHC)-peptide complex, TCEs bypass this step by directly linking CD3 on T-cells to tumor-specific antigens.¹⁹ It is important to note that TCEs preferentially activate CD8+ cytotoxic T-cells, which are the primary effectors in direct tumor cell killing. CD4+ helper T-cells are also recruited. However, they mainly serve supportive roles by releasing cytokines that amplify the immune responses. This dual involvement of CD4+ and CD8+ T-cells ensures a robust anti-tumor response independent of MHC compatibility.²¹ Simultaneously, CD4+ T-cells secrete several cytokines, including IL-2 and IFN- γ , which further stimulate T-cell proliferation and enhance recruitment to the tumor microenvironment.²⁰ Thus, unlike natural immune responses, which are dependent on MHC-peptide interactions, TCE-mediated cytotoxicity offers a universal approach to targeting tumor cells, which overcomes the heterogeneity often observed in tumor antigen presentation.²²

Targets of TCEs

The ideal TCE identifies a target ubiquitously expressed in the tumor cell and not expressed in low density in normal cells and tissues. In MM, several targets have been identified as candidates for therapeutic TCEs, such as the following:

- A. BCMA, B-cell maturation Antigen, is a well-recognized target for TCEs and CAR-T cells since it is present on the surface of plasma cells and minimally on other hematologic cells but absent in non-hematologic tissues. Its expression increases with MM progression, and sBCMA levels correlate with plasma cell burden and prognostic outcomes. Also, sBCMA levels correlate with therapy resistance, particularly in patients treated with BCMA-targeted therapies and those receiving standard regimens like proteasome inhibitors and immunomodulatory agents.^{23,24} Declining sBCMA levels indicate disease response, making it useful for monitoring non-secretory MM.²⁵ As a result, several clinical-grade TCEs, such as teclistamab, AMG 701, elranatamab, ABBV-383, REGN5458, and CC-93269, have been evaluated for use in patients with MM in clinical trials.
- B. GPRC5D, G Protein-Coupled Receptor, Class C, Group 5, Member D, is another cell surface antigen target for TCEs and CAR-T therapies in MM.²⁶ It is a transmembrane protein with no known ligand. In addition to its presence on plasma cells, it is found in hard keratinized tissue. GPRC5D mRNA is abundant in MM cell lines but

low in other malignancies.⁴ Several clinical-grade TCEs, such as talquetamab and formitamig, have been evaluated for use in clinical trials in patients with MM.

- C. FcRH5, Fc Receptor-Like 5, is a protein belonging to the Fc receptor homolog family. It is also known as FcRL5 or CD307 and is expressed exclusively in B cells and retained in normal and malignant plasma cells. It has no known high-affinity ligand or clear function. Besides MM, FcRH5 is also present in several B-cell malignancies.⁴ Cevostamab is a clinical-grade TCE evaluated for use in clinical trials in patients with MM.

Additional antigen targets of interest for TCE development in MM include CD38, SLAMF7, and CD19.

BCMA-Targeting TCEs

Teclistamab and Elranatamab

Teclistamab

Teclistamab was utilized to treat patients with relapsed and refractory MM (RRMM). It has a dual target effect on BCMA on MM and CD3 on T cells. The MajesTEC-1 study was a Phase 1/2 clinical trial that evaluated the efficacy and safety of teclistamab in RRMM patients who had received at least three previous treatments, including proteasome inhibitors, immunomodulatory drugs, and anti-CD38 monoclonal antibodies.²⁷ The study had two parts: dose escalation to identify the appropriate dose and dose expansion to assess the treatment's efficacy at the recommended Phase 2 dose (RP2D) of 1.5 mg/kg, which was injected subcutaneously weekly. Those who had a complete response (CR) for 6 months in the phase 2 portion of the study were eligible to receive the treatment at a lower dose of 1.5 mg/kg every two weeks until unacceptable toxicity or progressive disease (PD) occurred. It demonstrated an overall response rate (ORR) of 63%, a very good partial response (VGPR), and a 39% experience of CR.²⁷ The median progression-free survival (PFS) was 11.4 months, and the median OS was 22.2 months.²⁸ Furthermore, patients, such as those with high-risk cytogenetics, showed impressive hematologic responses. Among the most frequent adverse effects (AEs) was cytokine release syndrome (CRS) in 72% of the patients, neutropenia in 70.9%, anemia in 52.1%, and thrombocytopenia in 40%.²⁷ Most patients experienced CRS limited to grades 1 and 2, with only one grade 3 episode documented. This condition was generally treated with supportive measures without requiring dose reduction. Other mild side effects included erythema at the injection site and fatigue, which were mostly mild to moderate.

Elranatamab

The MagnetisMM-1 trial assessed the efficacy and safety of elranatamab for patients with RRMM. The trial is a multicenter, open-label study designed as a Phase 1/2 study.²⁹ The study is divided into dose escalation (Phase I) and dose expansion (Phase II). During the dose escalation phase, patients receive higher doses of elranatamab to establish the maximum tolerated dose (MTD) and the RP2D. The dose expansion phase evaluated the RP2D in a wider group of patients to obtain more comprehensive information on the efficacy and safety of the treatment. During Phase I of the MagnetisMM-1 trial, 55 patients received elranatamab at doses ranging from 215 to 1000 µg/kg subcutaneously, either weekly or every two weeks. With a median follow-up duration of 12 months, the confirmed ORR was 63.6%, with a CR of 38.2%. The median PFS was 11.8 months, and the median OS was 21.2 months.²⁹ Among patients who had previously undergone BCMA-directed therapy, 54% experienced positive treatment outcomes. Treatment-related AEs were observed in ≥ 33% of the patients. Neutropenia was the most common hematological AE at 74.5%, anemia at 67.3%, and lymphopenia at 52.7%. The most common non-hematological AE was CRS in 87.3% of patients; these were limited to grade 1 or 2 and were effectively manageable with supportive measures.²⁹ Part 2 of the MagnetisMM-1 Phase I trial examined the efficacy of elranatamab in combination with other agents, including dexamethasone, lenalidomide, and pomalidomide.

GPRC5D-Targeting TCEs

Talquetamab

Talquetamab, a TCE specifically targeting GPRC5D and CD3, has shown great potential as a treatment for patients with RRMM.²⁶ It uses a bispecific IgG4 antibody format specifically engineered to minimize Fc-receptor interaction and

efficiently mobilizes T-cells to target and eradicate myeloma cells expressing GPRC5D. The phase 1 MonumenTAL-1 trial evaluated the efficacy and safety of talquetamab in patients with RRMM.²⁶ A total of 288 patients were enrolled in the trial, with 47 participating in the phase 1 component. Each patient received at least an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent. In part 1 of the trial, two doses of talquetamab were selected for further investigation. Patients were divided into two groups: group 1 received 0.4 mg/kg administered weekly, and group 2 received 0.8 mg/kg every other week. All subjects encountered at least one AE in both groups. Severe AEs, leading to hospitalization, death, or life-threatening illness, were experienced by 43% of the patients who received 0.4 mg/kg and 34% of the patients who received 0.8 mg/kg. In the MonumenTAL-1 trial, talquetamab showed promising results in heavily pretreated MM patients, with an ORR of 71.7% at a median follow-up of 12.7 months for the 800 mcg/kg dose and 74.1% at 18.8 months for the 405 mcg/kg dose.^{26,30} The median PFS was 14.2 months for the higher dose and 7.5 months for the lower dose, while the median OS has not yet been reached.^{26,31} Notable AEs included CRS in 78% of patients, infections in 63% (22% being grade 3 or 4), and neutropenia in 38% (26% reaching grade 3 or 4).³⁰ Also, Talquetamab treatment is associated with dermatologic toxicities, including rash (67%), pruritus (25%), and nail changes (30–57%). GI toxicities such as dysgeusia (60%), xerostomia (30–57%), and dysphagia occur frequently. Weight loss was observed in 30–32% of patients. These AEs are usually mild to moderate but require supportive care.^{26,32,33}

Tables 1 and 2 summarize all the clinical trial outcomes and common AEs of the FDA-approved anti-BCMA and anti-GPRC5D TCEs.

Management of Toxicities of TCEs

Cytokine Release Syndrome (CRS)

CRS is a systemic inflammatory response that can occur after immunotherapies, including TCEs and CAR-T cell therapies. It is characterized by the rapid release of cytokines into the bloodstream by immune cells, resulting in a wide range of symptoms, from mild influenza-like to life-threatening conditions. The pathophysiology of CRS involves

Table 1 Summary Table of Clinical FDA-Approved TCEs

TCE	Target	Mechanism of Action	Clinical Outcomes	Patient Population
Teclistamab	BCMA	Engages CD3 on T cells and BCMA on MM cells to activate T cells for MM cell lysis	ORR: ~63%; Median PFS: 11.3 months (MajesTEC-1)	Relapsed/refractory MM patients, heavily pretreated with multiple prior therapies
Elranatamab	BCMA	Engages CD3 on T cells and BCMA on MM cells to activate T cells for MM cell lysis	ORR: ~64%; Median PFS: 11.8 months (MagnetisMM-1)	RRMM patients with at least three prior lines of therapy
Talquetamab	GPRC5D	Engages CD3 on T cells and GPRC5D on MM cells to activate T cells for MM cell lysis	ORR: ~71%; Median PFS: 14.2 months (MonumenTAL-1)	Patients with RRMM and prior exposure to PIs, IMiDs, and anti-CD38 antibodies

Table 2 Summary of Incidence and Management of Adverse Events in TCE Therapy

Adverse Event	Incidence	Management Strategies
Cytokine release Syndrome (CRS)	40–80%	Step-up dosing, tocilizumab, corticosteroids
ICANS (Neurotoxicity)	10–30%	Corticosteroids, anti-seizure prophylaxis
Infections	50–70%	IVIg prophylaxis, antimicrobial therapy
Skin Toxicities	30–60%	Topical steroids, antihistamines
GI Toxicities	20–50%	Dietary modification, supportive care

the stimulation and proliferation of T cells and other immune effector cells, leading to the subsequent production of a series of pro-inflammatory cytokines, such as interleukin-6 (IL-6), interferon-gamma (IFN- γ), and tumor necrosis factor-alpha (TNF- α).^{34,35} The abrupt increase of these cytokines in the bloodstream leads to the systemic inflammatory reaction that defines CRS. The severity of CRS can be influenced by the amount and type of cytokines released, the patient's initial health condition, and the unique attributes of the BsAb therapy. CRS is graded using the American Society for Transplantation and Cellular Therapy (ASTCT) criteria.³⁶ The management of CRS depends on the grade, primarily focusing on a combination of supportive care and targeted treatments to control the inflammatory response.³⁷ Grade 1 may only need symptomatic treatment, such as antipyretics for fever and fluids. For Grade 2 and above, dexamethasone and IL-6 receptor antagonists such as tocilizumab reduce cytokine levels and mitigate inflammation. Patients require hospital care with close monitoring, especially in severe cases, to manage complications such as hypotension, hypoxia, neurotoxicity, and organ dysfunction.³⁸ Timely identification and immediate action are crucial in effectively controlling CRS and minimizing its impact on TCE therapy patients. Tailoring the management strategy based on the intensity of symptoms and underlying patient factors can enhance results and allow patients to continue their treatments with minimal interruptions.

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

ICANS is a notable and intricate neurological consequence that occurs in patients receiving treatment with TCEs. This condition occurs when T lymphocytes are activated and multiply in response to BsAbs, resulting in the release of pro-inflammatory cytokines such as interleukin-6 (IL-6), interferon-gamma (IFN- γ), and tumor necrosis factor-alpha (TNF- α). Cytokines breach the blood-brain barrier, enabling immune cells and inflammatory mediators to enter the central nervous system (CNS), resulting in neurotoxic symptoms. While ICANS is primarily attributed to T-cell activation and cytokine-driven inflammation, its precise pathogenesis remains unclear. Additional factors, such as direct immune cell-mediated neurotoxicity or microglial activation, may also play a role in its development.^{39,40} The clinical presentations of ICANS exhibit a broad range of symptoms, spanning from minor cognitive impairment and involuntary muscle contractions to severe manifestations such as aphasia, epilepsy, and cerebral edema. The initiation of symptoms usually happens early during therapy, usually during the initial week. However, the precise time and intensity of these symptoms vary based on the specific TCE employed, its dosing schedule, and the patient's overall health condition. As imaging studies such as MRI and CT scans are often insignificant except in ruling out CNS infections, the diagnostic criteria for ICANS mostly depend on clinical evaluation and detection of distinctive symptoms. Timely recognition and immediate action are essential to prevent severe ICANS. A severity grading system, which is frequently combined with CRS assessment, guides therapy decisions.^{39,40} Grade 1 ICANS may only need supportive care, but grade ≥ 2 ICANS usually requires the start of dexamethasone therapy. This treatment involves administering 10–20 mg of dexamethasone intravenously every 6 hours, followed by a gradual reduction in dosage once symptoms improve. Convulsions are treated using anti-epileptic drugs such as levetiracetam. In severe situations, substantial doses of corticosteroids such as IV methylprednisolone (1 g/day) may be required for at least 3 days until symptoms improve. Management options may involve temporary cessation of TCEs until the resolution of ICANS symptoms and supportive care measures, such as hydration management and neuro monitoring.

Infections

At baseline, patients with RRMM are at a significant risk for infection due to immune dysfunction from the disease. However, the mechanism of action of these TCEs can also result in immune system dysfunction, making patients vulnerable to a range of infections. Bacterial infections are common, accounting for 45% of all infections.^{41,62} These infections range from mild conditions to severe ones, such as pneumonia and sepsis, which can eventually lead to death. Viral infections are usually due to the reactivation of herpes viruses and cytomegalovirus (CMV), occurring in 49% of cases.^{41,42} Aspergillosis, invasive fungal infection, and other fungal infections, while less common, present a substantial risk due to their high morbidity and mortality rates in individuals with immune dysfunction, occurring in approximately 6% of cases.⁴¹ Thus, in patients receiving TCEs, prophylactic measures are essential in mitigating the risk of infection. Prophylactic antimicrobial therapy is a standard approach to prevent opportunistic infections. Another important measure to reduce the risk of infection is to vaccinate patients before the initiation of treatment, such as with

influenza and pneumococcal vaccines, to enhance the patient's immune system. Patients should be monitored regularly for any signs of infection, and prompt interventions are essential components of infection management. Studies have shown that following these prophylactic measures can reduce the incidence of severe infections by 50%. Another form of treatment is Intravenous immunoglobulin (IVIg), which has been associated with a significant reduction in the incidence of serious infections in MM patients receiving anti-BCMA bispecific antibodies.⁴³ The findings suggest that IVIg can lower the risk of grade 3 to 5 infections by as much as ten-fold, addressing the profound immunodeficiency in these patients.⁴³ This highlights IVIg's potential as an effective strategy to mitigate the heightened risk of severe infections during treatment.⁴⁴

Skin Toxicities

Skin toxicities have been recorded in a substantial portion of patients treated with Talquetamab during the MonumentAL-1 trial. Skin toxicity was around 67%, with most AEs ranging from Grade 1/2. The common manifestations included rash, pruritus, and dermatitis. Skin-related AEs varied in severity. Approximately 30–40% of skin toxicities presented as rash, often characterized as maculopapular eruptions that could be diffuse and accompanied by pruritus. Pruritus was experienced in approximately 25% of the patients, causing significant discomfort and impacting daily activities. Grade 3 rashes were observed under specific dosages. Notably, there were no reports of grade 3 rash-related AEs at the 405- μ g dose level, but they occurred in 16% of patients at the 800- μ g dose level. Grade 3 rashes were necessitated and were sensitive to oral and topical glucocorticoid treatments.²⁶ Management of severe cases often required systemic corticosteroids, highlighting the need for vigilant monitoring and timely intervention. Nail-related AE events were also significant. At the dose level of 405 μ g, 57% of patients experienced nail-related toxicities, and 27% at the 800- μ g dose level.^{26,27} These events included nail discoloration, brittleness, and onycholysis. The management of these AEs usually involves symptomatic treatment using topical agents and/or antihistamines, but more severe cases may require systemic corticosteroids.⁴⁵ In managing skin toxicities among patients receiving talquetamab, vigilant monitoring and proactive intervention are crucial to minimizing side effects while maintaining therapeutic efficacy. Further studies are essential to understand the mechanisms behind these toxicities and to develop strategies for their prevention or minimization.

Gastrointestinal Toxicities

Talquetamab is linked to several gastrointestinal (GI) side effects in addition to oral-related problems. The AEs reported are mainly of grade 1 or 2 severity and include dysgeusia (change in taste perception), xerostomia (dry mouth), dysphagia (difficulty swallowing), constipation, diarrhea, and nausea.³² Around 60% of patients report these taste changes shortly after starting the treatment. Xerostomia, also known as dry mouth, affects a substantial percentage of individuals, ranging from 30% to 57%, at various dosage levels.³³ Dysphagia, albeit less common, is also observed. During clinical studies, a significant proportion of patients who received talquetamab experienced a reduction in weight. A drop in weight was recorded by 30% of patients who received a dose of 405 μ g and 32% of patients who received a dose of 800 μ g.²⁶ In addition to these fluctuations in weight, gastrointestinal problems such as constipation, diarrhea, and nausea have been recorded. Effectively addressing gastrointestinal toxicity linked with talquetamab requires taking preventive steps.⁴⁵ Patients should be provided with supportive care, which includes making dietary adjustments and administering medications to ease symptoms such as constipation and diarrhea. It is crucial to regularly assess weight and nutritional condition and modify weight-based drugs as necessary.

Sequencing Strategies with Other Anti-BCMA Therapies

The strategic sequencing of treatments has become increasingly critical with the emergence of multiple BCMA-targeted therapies, including belantamab mafodotin and CAR-T cell therapies. A key challenge across these modalities is the development of resistance mechanisms, such as antigen escape.⁴⁶ Evidence suggests that prior exposure to BCMA-directed therapies can influence the efficacy of subsequent treatments, as antigen loss or downregulation following initial therapy may compromise the effectiveness of later BCMA-targeted interventions.⁴⁶ Alternative sequencing strategies are under investigation to mitigate these challenges. These include the use of agents targeting distinct antigens, such as GPRC5D or FcRH5, and the exploration of combination therapies designed to prevent or overcome resistance.⁴⁷

Mechanisms of Resistance to BCMA TCEs

TCEs targeting BCMA have significantly advanced the treatment landscape of MM. However, resistance to these therapies remains a substantial challenge, necessitating a deeper understanding of the underlying mechanisms to optimize treatment efficacy.

1. *Antigen Escape*: A primary resistance mechanism involves the deletion or downregulation of BCMA on multiple myeloma cells, a phenomenon known as antigen escape. This alteration compromises the binding affinity of TCEs, diminishing their therapeutic effectiveness. Although infrequent, studies have documented cases where BCMA target loss leads to resistance against BCMA-directed therapies.⁴⁸
2. *T-Cell Exhaustion and Dysfunction*: Chronic activation of T cells by TCEs can induce T-cell exhaustion, characterized by diminished effector functions and sustained expression of inhibitory receptors. This exhausted state weakens the immune system's ability to effectively eliminate myeloma cells, ultimately reducing the efficacy of TCE therapies.⁴⁹
3. *Tumor Microenvironment (TME) Factors*: The immunosuppressive nature of the MM tumor microenvironment plays a pivotal role in resistance to TCE therapies. Regulatory T cells, myeloid-derived suppressor cells, and immunosuppressive cytokines such as TGF- β and IL-10 hinder T-cell activation and proliferation. As a result, TCE-redirectioned T cells exhibit impaired functionality within the hostile TME, limiting their therapeutic impact.⁴⁹

Addressing these resistance mechanisms through novel therapeutic strategies, including alternative antigen targets, combination approaches, and interventions to modulate the TME, is essential for enhancing the durability and effectiveness of BsAb-based treatments in MM.

Strategies to Overcome TCE Resistance

1. *Utilizing combination therapies*: BsAbs combined with medicines that modify the TME or boost the function of T-cells, including immune checkpoint inhibitors, show potential for recovering T-cell activity and increasing treatment responses in multiple myeloma. This combo method seeks to overcome insufficient T-cells by exploiting the synergistic benefits of both treatment approaches.⁵⁰
2. *Targeting multiple antigens*: Developing TCEs that target multiple antigens simultaneously, such as GPRC5D and BCMA, can reduce the chance of antigen escape. This dual-targeting method could also improve therapy efficacy by targeting tumor heterogeneity and lowering the likelihood of resistance development.⁵¹
3. *Inhibition of γ -Secretase*: Inhibiting γ -secretase has been demonstrated to limit the breakdown of BCMA from the surface of MM cells. This reduces soluble BCMA and increases BCMA density in MM cells, leading to an increase in the binding and effectiveness of BCMA-targeted treatment options, such as TCE.⁵²

Ongoing studies aim to understand better how these resistance mechanisms will create more effective therapy regimens and enhance outcomes for MM patients.

Future Directions

TCEs have revolutionized the treatment of RRMM, offering hope to patients who have exhausted conventional options. Future advancements focus on enhancing targeting specificity, identifying novel MM-selective antigens, and mitigating associated toxicities such as CRS and on-target, off-tumor effects. Some strategies to reduce AEs include engineering lower-affinity TCEs, optimizing dosing schedules, and integrating predictive biomarkers for personalized treatment. Clinical trials are expanding TCE applications beyond RRMM, exploring their role in newly diagnosed MM (NDMM) and high-risk smoldering MM (SMM). Notable studies include teclistamab plus daratumumab (NCT05083169), elranatamab in transplant-eligible NDMM (NCT05317416), and BsAb-CD38 combinations like teclistamab plus isatuximab (NCT04557098).

Resistance to TCEs remains a major challenge, manifesting as either primary (inherent) or acquired resistance. About one-third of RRMM patients exhibit primary resistance, while most responders eventually develop disease progression.

Investigating tumor-intrinsic factors, the tumor microenvironment, and T-cell fitness is critical to improving immunotherapy efficacy. Dual-antigen targeting, exemplified by the RedirectTT-1 trial (NCT04586426) combining talquetamab (GPC5D-targeting BsAb) and teclistamab (BCMA-targeting BsAb), is one such strategy that aims to overcome resistance mechanisms.⁴⁷

As molecular insights into MM deepen, TCEs may be integrated earlier in treatment, potentially as frontline therapy or in targeting MRD to reduce relapse risk and enhance long-term survival. With ongoing research addressing current limitations, the next generation of TCEs is poised to play a central role in transforming MM treatment.

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Disclosure

The authors declare no competing interests in this work.

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