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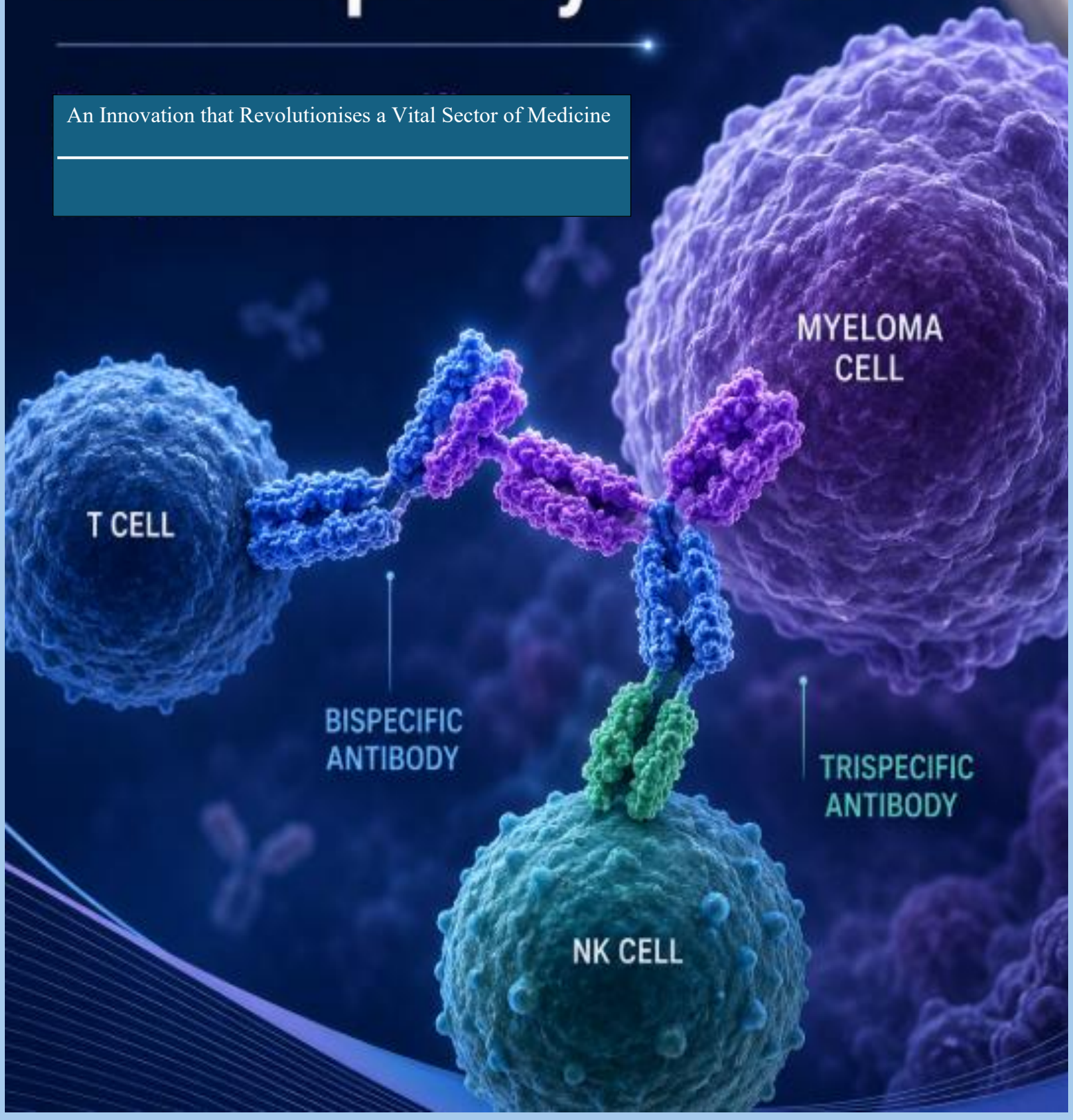
Emerging Immunotherapy in Multiple Myeloma:

An Innovation that Revolutionises a Vital Sector of Medicine



Emerging Immunotherapy in Multiple Myeloma:
Evaluating Bispecific and Trispecific Antibodies

Introduction

In 2022, a 68-year-old retired teacher in Adelaide experienced her fourth relapsed multiple myeloma. She had exhausted three classes of treatment. Her oncologist had nothing new to offer, until a clinical trial opened. Her story reflects the experience of many Australians living with relapsed multiple myeloma and illustrates one of the greatest challenges in treating this disease (Cancer Australia, 2024).

Multiple myeloma is a cancer of plasma cells, the immune system's antibody-producing cells. When plasma cells become malignant, they accumulate in the bone marrow, crowd out healthy blood cell production, and generate excessive amounts of a non-functional protein called M protein. The result is destructive bone lesions, kidney failure, anaemia, and a severely weakened immune system (Rajkumar, 2022). Around 2,755 Australians were diagnosed in 2025, and a recent modelling study projects that nearly 80,000 will develop the disease between 2019 and 2043 (Cancer Australia, 2024; Luo *et al.*, 2024).

Five-year survival has more than doubled from 28% in the late 1980s to 61% today, yet the disease remains incurable (Cancer Australia, 2024). Nearly all patients eventually experience disease relapse. Patients who exhaust proteasome inhibitors, immunomodulatory drugs, and anti-CD38 antibodies, termed triple-class refractory disease, historically survived approximately six to nine months on available options (Rajkumar, 2022). For these patients, medicine urgently needed something fundamentally different. This report examines how bispecific and trispecific T-cell engaging antibodies work, how they have influenced science and society, and what their applications and limitations reveal about the future of cancer treatment.

Mechanism of Action of Bispecific T-Cell Engaging Antibodies

The immune system already contains cells capable of killing cancer, specifically cytotoxic T lymphocytes. However, myeloma cells escape immune recognition by reducing the expression of molecules required for effective T-cell activation. Bispecific T-cell engaging antibodies (TCEs) bypass this entirely. One arm of the antibody binds to a protein on the myeloma cell surface, while the other arm binds to the T cell's activation receptor, CD3. By physically bringing the two cells together, the T cell activates and destroys the cancer cell without requiring prior immune recognition (Gonsalves *et al.*, 2024).

This bridging triggers a signalling cascade inside the T cell that drives it to release lytic granules directly onto the myeloma cell. These granules contain perforin, which punches pores in the myeloma cell's membrane, and granzyme B, which slips through those pores and activates the cell's own self-destruction programme, known as apoptosis (Mechanistic Insights, 2025). Because this process does not rely on the myeloma cell presenting its own antigens, the cancer's primary immune evasion strategy is rendered irrelevant.

Three myeloma surface proteins have become the main targets. BCMA is highly expressed on virtually all myeloma cells, where it drives survival signalling. GPRC5D is present at even higher density, approximately 20,600 receptor copies per myeloma cell, while being almost entirely absent on healthy tissue (Carlo-Stella *et al.*, 2023). FcRH5 is expressed uniformly across all myeloma cells regardless of prior therapies received (Gonsalves *et al.*, 2024). Together, these targets provide clinicians with genuinely independent therapeutic options, and that independence proves critical to the next generation of treatment.

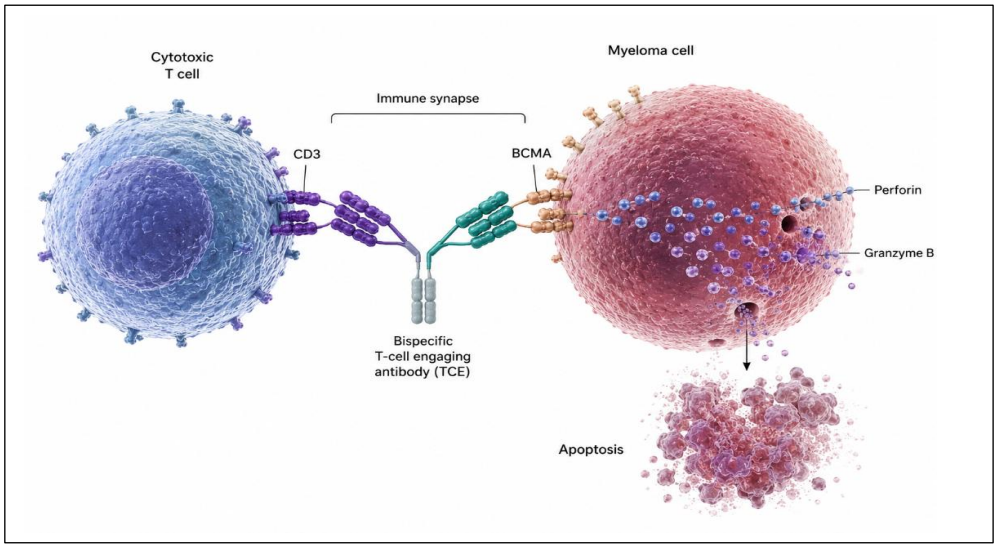


Figure 1. The antibody simultaneously binds BCMA on the myeloma cell and CD3 on the T cell, forcing an immune synapse. Perforin creates pores in the myeloma membrane; granzyme B then triggers apoptosis, without any prior immune recognition of the cancer cell. Original diagram based on Mechanistic Insights (2025) and Gonsalves et al. (2024).

Table 1: Myeloma Cell Surface Targets Used by Bispecific and Trispecific Antibodies

Target	Density on Myeloma Cells	Normal Tissue Expression	Approved Agents
BCMA	High; activates cell survival signalling	Mature B cells only	Teclistamab, Elranatamab
GPRC5D	Very high (~20,600 copies/cell)	Hair follicles only	Talquetamab, JNJ-79635322
FcRH5	Uniform; maintained after prior therapy	B-cell lineage	Cevostamab (Phase I/II)

Table 1: The three principal immunotherapy targets on myeloma cells and their clinical significance. Sources: Gonsalves et al. (2024); Carlo-Stella et al. (2023).

How Have These Antibodies Influenced Science and Society?

The development of bispecific antibodies has reshaped fields well beyond oncology. Early bispecific antibodies were limited by their short circulating half-life, as their small size meant the body cleared them from the bloodstream within hours, requiring continuous intravenous infusion. Scientists resolved this by incorporating the antibody's Fc tail region, which the body naturally

recycles, extending the drug's effective lifespan to more than ten days and making outpatient subcutaneous injection possible (Gonsalves *et al.*, 2024). This engineering advance, enabled by cryo-electron microscopy and now accelerated by artificial intelligence antibody modelling, transformed a laboratory concept into a practical medicine accessible to patients outside major hospitals.

Research into treatment resistance has also transformed immunological understanding. Scientists discovered that myeloma creates a profoundly immunosuppressive environment inside the bone marrow, filled with cells and chemical signals that actively suppress T-cell function. This explains why simply having functional T cells is not enough (Parrondo *et al.*, 2024). That insight, driven by the need to explain bispecific resistance, is now informing combination therapy strategies across many cancers. Resistance to one technology became the scientific catalyst for the next generation.

The impact on patients has been rapid and measurable. Before bispecific antibodies, Australians with triple-class refractory myeloma faced a median survival of approximately six to nine months. Teclistamab, the first approved BCMA-directed bispecific antibody, significantly changed this: in the pivotal MajesTEC-1 trial of 165 patients with heavily pretreated disease, 63% responded and median overall survival reached 18.3 months, more than double the historical benchmark (Moreau *et al.*, 2022; Garfall *et al.*, 2024). These are not abstract statistics. They represent patients who returned to their families and their lives.

These drugs have also changed who can access advanced cancer care in Australia. Unlike CAR-T cell therapy, which requires manufacturing over four to eight weeks and treatment at one of only a handful of licensed Australian centres, bispecific antibodies are administered as a subcutaneous injection in outpatient clinics. Critically, elranatamab was listed on the Australian Pharmaceutical Benefits Scheme (PBS) on 1 April 2026, meaning eligible Australian patients now pay only standard PBS co-payments rather than approximately AUD $5,000 per script without subsidy (Australian Government Department of Health, 2026). This listing represents a pivotal achievement in equitable access, ensuring that the survival benefits demonstrated in clinical trials can be realised by Australian patients, including those outside major cities.

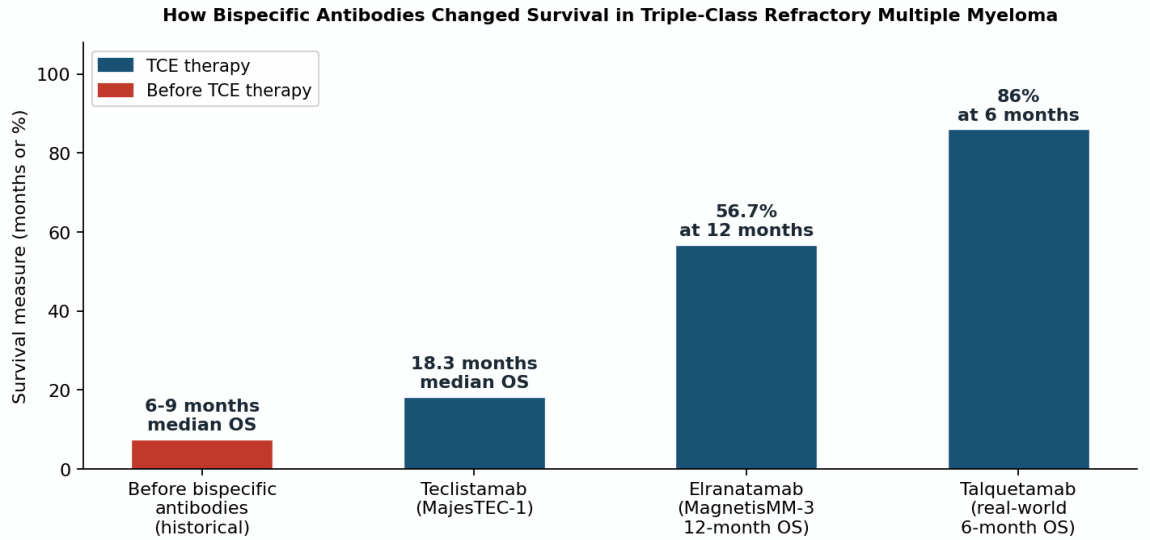


Figure 2. Survival outcomes with approved bispecific antibody therapy compared with historical triple-class refractory myeloma prognosis of six to nine months median overall survival. Sources: Moreau et al. (2022); Garfall et al. (2024); Rodriguez-Otero et al. (2023); Nature Blood Cancer Journal (2025).

Clinical Applications and Limitations

Three bispecific antibodies are now approved and in clinical use for relapsed myeloma: teclistamab, elranatamab (both BCMA x CD3), and talquetamab (GPRC5D x CD3). Elranatamab achieved a 61% response rate and a 12-month overall survival of 56.7% in the MagnetisMM-3 trial (Rodriguez-Otero *et al.*, 2023). Talquetamab, targeting the more abundant GPRC5D receptor, achieved a 73% response rate in a 2025 real-world study of 114 patients, most of them penta-refractory, meaning they had exhausted five prior drug classes (Dhodapkar *et al.*, 2025). Because GPRC5D remains present on myeloma cells even after BCMA-directed therapy fails, these two antibodies can be used sequentially, providing patients with a second independent line of bispecific treatment.

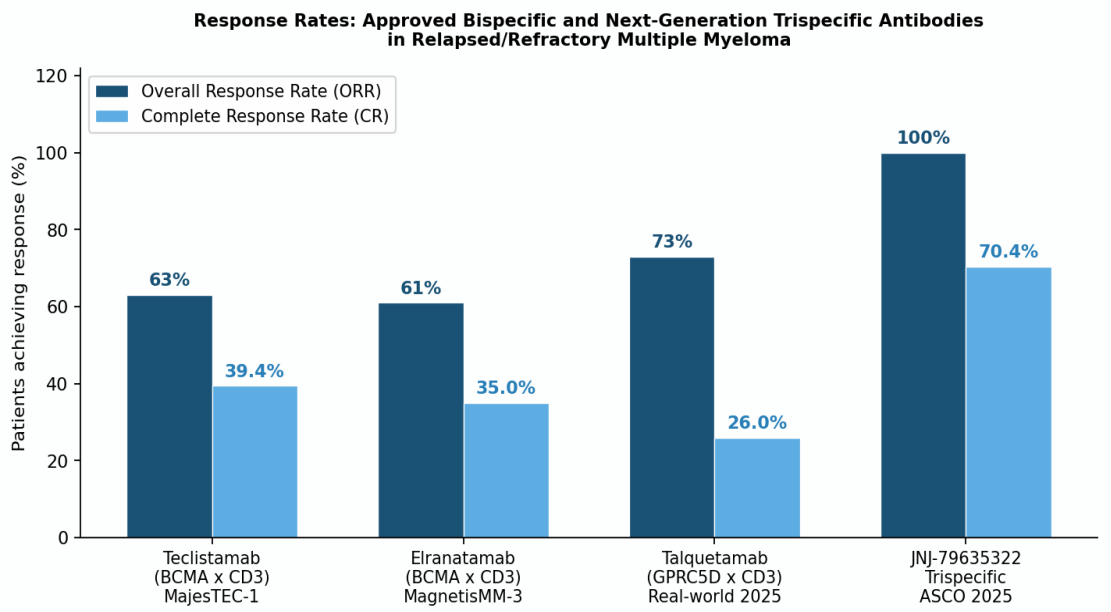


Figure 3. Overall and complete response rates for the three approved bispecific antibodies and the next-generation trispecific JNJ-79635322 in relapsed/refractory myeloma. The trispecific agent, targeting two myeloma antigens simultaneously, reported up to 100% response rates at ASCO 2025, suggesting dual-antigen engagement may substantially reduce the likelihood of resistance. Sources: Moreau et al. (2022); Rodriguez-Otero et al. (2023); Dhodapkar et al. (2025); Bahlis et al. (2025).

Despite these results, a consistent biological problem emerges: antigen escape. Under the pressure of effective targeted therapy, myeloma cells evolve. Subclones that have lost or mutated the target antigen survive and repopulate the tumour. Single-cell genomic sequencing of patients who relapsed after bispecific therapy has confirmed this mechanism repeatedly (Parrondo *et al.*, 2024). It is an inherent vulnerability of targeting only one antigen at a time, and it directly motivated the development of trispecific antibodies.

A second problem is specific to BCMA-targeted agents. An enzyme called gamma-secretase constantly releases the BCMA protein from the myeloma cell surface into the bloodstream. This circulating soluble BCMA competes with the tumour cell for the antibody drug, reducing effective treatment levels before the drug reaches its target (Parrondo *et al.*, 2024). Scientists are now

trialling gamma-secretase inhibitors alongside bispecific antibodies to restore full target availability.

The most common side effect is cytokine release syndrome, a temporary but sometimes severe inflammatory reaction when T cells activate in large numbers. In MajesTEC-1, 72% of patients experienced cytokine release syndrome, although severe grade 3 or higher episodes occurred in only 0.6%, largely due to step-up dosing protocols that gradually increase exposure over one week (Moreau *et al.*, 2022). A more persistent concern is infection: bispecific antibodies deplete normal plasma cells that produce protective antibodies, leaving patients immunocompromised for months. Roughly 40% of patients in clinical trials experienced serious infections, requiring preventive antibiotics and immunoglobulin replacement.

Despite the PBS listing of elranatamab in Australia, global access remains a profound challenge. For patients in low- and middle-income countries, where these drugs carry costs equivalent to tens of thousands of Australian dollars per month, PBS-style subsidy schemes do not exist. PBS listing decisions will determine whether clinical trial efficacy translates into real-world clinical access for all patients, and international frameworks for outcomes-based pricing are urgently needed.

Table 2: Clinical Results for the Three Flagship Approved Bispecific Antibodies

Agent	Target	Key Trial	ORR / CR	OS Outcome
Teclistamab	BCMA x CD3	MajesTEC-1 (n=165)	63% / 39%	18.3 months median OS
Elranatamab	BCMA x CD3	MagnetisMM-3 (n=123)	61% / 35%	56.7% alive at 12 months
Talquetamab	GPRC5D x CD3	Real-world 2025 (n=114)	73% / 26%	86% alive at 6 months

Table 2: Flagship approved bispecific antibodies and key clinical outcomes. ORR = overall response rate; CR = complete response. Sources: Moreau et al. (2022); Rodriguez-Otero et al. (2023); Dhodapkar et al. (2025).

Table 3: Key Limitations and Current Strategies to Address Them

Limitation	What Happens	How Scientists Are Responding
Antigen escape	Myeloma cells lose the target protein under treatment pressure	Trispecific antibodies co-targeting two antigens simultaneously; sequential therapy
Soluble BCMA sink	Circulating BCMA mops up the drug before it reaches tumour cells	Gamma-secretase inhibitor combination to block BCMA shedding
Cytokine release syndrome	Mass T-cell activation triggers systemic inflammation	Step-up dosing; tocilizumab; corticosteroids
Infection risk	Normal plasma cell depletion leaves patients immunocompromised	Prophylactic antibiotics; immunoglobulin replacement therapy

Limitation	What Happens	How Scientists Are Responding
Global access inequity	High drug costs; limited to high-income health systems	PBS listing; outcomes-based pricing; international access frameworks

Table 3: Principal limitations of bispecific antibody therapy and current approaches to address them. Sources: Parrondo et al. (2024); Moreau et al. (2022).

Why Trispecific Antibodies Represent the Next Step in Myeloma Therapy

Antigen escape is not a flaw in the concept of bispecific antibodies. It is the predictable evolutionary response of cancer under sustained selection pressure. Once scientists understood that, the logical question became clear: what if the antibody targeted two independent myeloma antigens at once, so that the cell would need to lose both simultaneously to escape? The probability of simultaneous loss of both antigens is significantly reduced. That reasoning is the foundation of the trispecific antibody (Bahlis *et al.*, 2025).

JNJ-79635322, targeting BCMA and GPRC5D simultaneously alongside CD3, is the most advanced example to date. In its first-in-human phase I clinical trial, patients who were naive to both BCMA- and GPRC5D-directed therapies reported up to 100% overall response rates at the recommended dose, with 70% achieving complete responses and 95% remaining progression-free at one year (Bahlis *et al.*, 2025). These results substantially surpass any single bispecific antibody in comparable patients and may significantly reduce the likelihood of resistance through the simultaneous engagement of two independent myeloma targets.

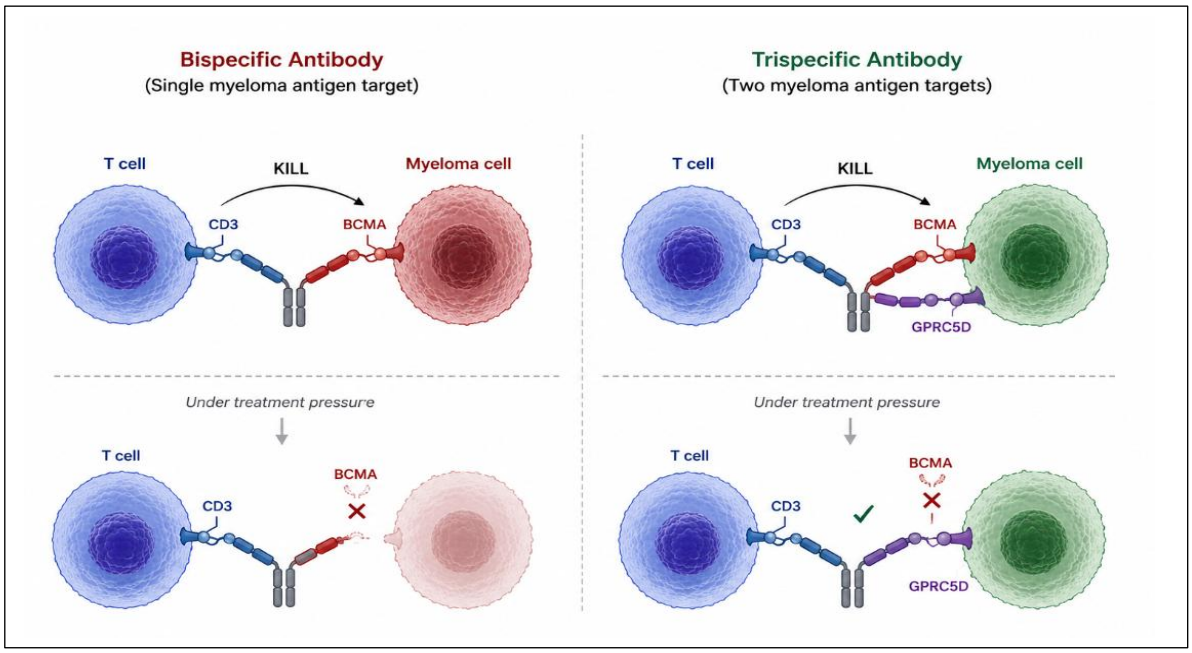


Figure 4. A myeloma cell can escape a bispecific antibody by losing BCMA (left panel). Escaping a trispecific requires the simultaneous, independent loss of both BCMA and GPRC5D (right panel), an event that is exponentially less probable. Original diagram based on Parrondo et al. (2024), Frontiers in Oncology.

Where Is This Technology Heading?

The most immediate shift is already underway. Bispecific antibodies are moving from late-line salvage therapy into earlier treatment. On 5 March 2026, the FDA approved teclistamab in

combination with daratumumab (Tec-Dara) for patients with at least one prior line of therapy, based on the MajesTEC-3 trial, which showed an 83% reduction in the risk of disease progression or death relative to the standard of care control arm (FDA, 2026; Johnson and Johnson, 2026). If ongoing trials confirm similar benefit in newly diagnosed patients, bispecific antibodies may potentially reduce the role of autologous stem cell transplantation in some patient groups, significantly restructuring how myeloma is treated globally.

Researchers are also combining bispecific antibodies with drugs that target the immunosuppressive environment inside the bone marrow, including PD-1 checkpoint inhibitors to reverse T-cell exhaustion caused by prolonged treatment (Parrondo *et al.*, 2024). Sequentially switching between BCMA-directed and GPRC5D-directed agents at relapse has already demonstrated preserved responses in real-world data (Dhodapkar *et al.*, 2025). The engineering principles developed for myeloma are now being translated to acute myeloid leukaemia and diffuse large B-cell lymphoma (Gonsalves *et al.*, 2024). A key unanswered question remains whether these deep molecular responses will ultimately translate into curative outcomes. That is the open scientific question at the frontier of this field.

Future Research Directions

Several scientifically justified research directions emerge directly from the limitations identified above. First, multi-antigen targeting strategies beyond the trispecific format are being explored, including quadrivalent antibody constructs and combinations of two independent bispecific antibodies administered concurrently, such as the RedirecTT-1 trial combining teclistamab and talquetamab, which achieved an 84% response rate in heavily pretreated patients (Bahlis *et al.*, 2025). Second, reversing T-cell exhaustion represents a fundamental biological challenge: research into treatment-free intervals, lower-dose maintenance schedules, and PD-1/LAG-3 checkpoint inhibitor combinations aims to restore T-cell functional capacity and prolong durable responses (Parrondo *et al.*, 2024).

Third, reducing the severity of cytokine release syndrome and infectious complications remains a clinical priority. Prophylactic tocilizumab administration before the first dose, refined step-up dosing algorithms, and novel anti-infective prophylaxis regimens are all under active investigation. Fourth, improving treatment access requires structural solutions. The elranatamab PBS listing in Australia on 1 April 2026 provides a model: outcomes-based pricing agreements, where pharmaceutical companies are reimbursed only for patients who respond, reduce financial risk for health systems while expanding access (Australian Government Department of Health, 2026). Extending similar frameworks internationally, particularly to low- and middle-income countries with rising myeloma incidence, represents one of the most pressing translational challenges in the field.

Conclusion

Multiple myeloma remains incurable with current therapies. But bispecific and trispecific antibodies are fundamentally changing what incurable means. They have transformed a disease where the most heavily treated patients could expect months of survival into one where complete, molecularly verified remissions are now routine outcomes in clinical trials. In doing so, they have

reshaped protein engineering, deepened understanding of the tumour immune environment, and demonstrated that the gap between laboratory biology and patient benefit can close faster than anyone expected.

The trispecific frontier, represented by the reported up to 100% response rates at ASCO 2025, shows that this science continues to accelerate. The challenges that remain, including infection risk, access inequity, and the unanswered question of cure, are not reasons for pessimism. They are the scientific problems that define the field's future. For the retired teacher in Adelaide who ran out of options, and for the hundreds of thousands of patients like her around the world, that future cannot come quickly enough.

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1560 words excluding references and captions.

Artificial Intelligence (AI) Declaration

Tools Used: ChatGPT (OpenAI) and Grammarly.

Description of Use:

- **ChatGPT:** This tool was used strictly during the initial pre-writing phase to brainstorm potential science topics, suggest relevant keywords for academic research, and help me break down complex scientific concepts. No text or sentences generated by ChatGPT were copied or used in the final submission.
- **Grammarly:** This tool was used exclusively during the final editing stage as a digital proofreader to check for standard spelling, punctuation, and typographical errors.