Exploring the Potential of Bispecific Antibodies in Multiple Myeloma

Author affiliation: Chandana G R

Abstract

Multiple myeloma (MM), is a challenging malignancy of clonal plasma cells accounting for over 10% of hematologic cancers. Its pathogenesis involves complex immune system dysfunction, leading to frequent disease relapse and diminished drug efficacy over time. In defiance of therapeutic advancements, MM patients often face cycles of remission followed by relapse, each cycle yielding progressively poorer outcomes and underscoring the urgent need for innovative treatments. The landscape of personalized immunotherapeutic strategies includes immune checkpoint inhibitors, monoclonal antibodies, antibody-drug conjugates chimeric antigen receptor T (CAR-T) cells CAR-natural killer (NK) cells, and notably, bispecific antibodies (BsAbs). BsAbs are designed to engage both T cells and malignant cells simultaneously, thereby activating cytotoxic T cells to target and destroy tumor cells.

Bispecific antibodies, which are currently at the forefront of clinical development, bind CD3 on T cells and plasma cell epitopes, such as B-cell maturation antigen (BCMA), G-protein coupled receptor family C group 5 member D (GPRC5d), and receptor homolog 5 (FcRH5). These antibodies are also exhibiting previously unheard-of response rates in patients with RRMM, including those with penta-refractory disease. Despite the promising potential of these therapies, multiple myeloma continues to challenge clinicians due to the development of resistance to conventional and current treatments. The relentless cycle of remission and relapse demands for new therapeutic strategies that can effectively harness the immune system to target multiple myeloma cells through innovative mechanisms. This review provides a comprehensive overview of BsAbs for multiple myeloma, offering key clinical insights, detailed mechanisms of action, and future research directions to combat this complex disease.

Keywords: *Multiple myeloma (MM), hematologic cancers, relapsed/refractory multiple myeloma (RRMM), bispecific antibodies (BsAbs), immune system dysfunction, drug resistance, innovative treatments, immune checkpoint inhibitors, monoclonal antibodies, antibody-drug conjugates, CAR-T cells, BCMA-targeting therapies, GPRC5d bispecific antibodies, FcRH5 plasma cell therapies, and mechanisms of action of BsAbs.*

Introduction:

The emergence of innovative agents like proteasome inhibitors (PI), immunomodulatory agents (IMiD), and anti-CD38 monoclonal antibodies (MoAb) has led to enhanced survival rates among patients diagnosed with multiple myeloma (MM) and is anticipated to further progress. Despite this, relapse is unavoidable, and subsequent remissions tend to be briefer due to the development of acquired drug resistance and the emergence of refractory disease. Patients classified as triple-class refractory (resistant to a PI, IMiD, and anti-CD38 MoAb) face a poor prognosis, demonstrating an overall response rate (ORR) of 31%, a median progression-free survival (PFS) of 3.4 months, and a median overall survival (OS) of 9.3 months with the subsequent treatment regimens post anti-CD38 MoAb failure. Furthermore, individuals with penta-refractory myeloma (resistant to lenalidomide, pomalidomide, bortezomib, carfilzomib, and an anti-CD38 MoAb) have an even inferior prognosis, with a median OS of approximately 6 months under subsequent therapies. Ineffective T-cell immunity has been linked to the

development of RRMM and disease advancement through T-cell anergy, exhaustion, and senescence. Nevertheless, investigations focusing on the endogenous T-cells of RRMM patients subjected to ex-vivo stimulation indicate that these T-cells can exhibit anti-myeloma cytotoxic activity once stimulated. Bispecific antibodies are therapeutic agents made to concurrently activate endogenous T cells and malignant cells by binding to a T-cell epitope (typically CD3) and an extracellular tumor antigen, thereby triggering cytotoxic T cell activity and the liberation of cytotoxic granules that cause tumor cell death. Bispecific antibodies targeting plasma-cell antigens such as B-cell maturation antigen (BCMA), G-protein coupled receptor family C group 5 member d (GPRC5d), and Fc receptor-homolog 5 (FcRH5) are extensively progressed in clinical development, with teclistamab, elranatamab (BCMA-targeting bispecific antibodies), and talquetamab (GPRC5d) already sanctioned by the FDA for RRMM after ≥4 or more lines of therapy, alongside other anti-BCMA and GPRC5d bispecific antibodies, and cevostamab (FcRH5 x CD3 bispecific antibody) in clinical development—the aim.

1.2 Mechanism of bispecific antibodies

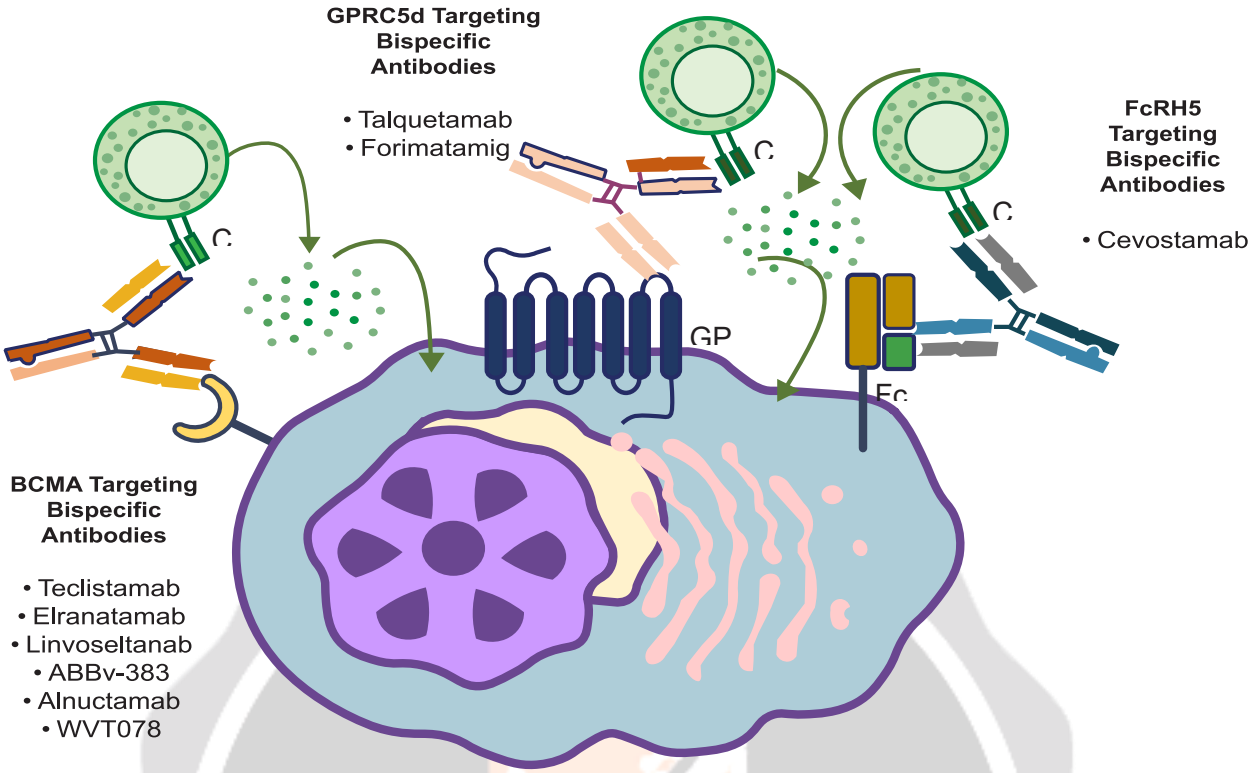
Bispecific antibodies (BsAbs) are a class of engineered monoclonal antibodies designed to simultaneously bind to two different epitopes or antigens. This dual-binding capability enables unique mechanisms of action that traditional monospecific antibodies cannot achieve, making them valuable in therapeutic applications, particularly in oncology, immunology, and infectious diseases.

Mechanistically, bispecific antibodies function by bringing two molecular targets into close proximity to facilitate biological interactions or disrupt pathological pathways. They are typically engineered to combine fragments of two distinct antibodies or through innovative scaffolding techniques, ensuring specificity and stability.

Key mechanisms include:

1. **Immune Cell Recruitment**: One arm of the bispecific antibody binds to a tumor-associated antigen (TAA) on cancer cells, while the other arm binds to an immune effector cell, such as a T-cell (via CD3) or natural killer (NK) cell. This promotes the targeted destruction of tumor cells through immune-mediated cytotoxicity.
2. **Signal Modulation**: Bispecific antibodies can bridge two signaling molecules, leading to activation, inhibition, or modulation of specific pathways, which is particularly useful in immune checkpoint modulation or receptor-ligand interactions.
3. **Dual Antigen Targeting**: BsAbs can simultaneously target two distinct antigens or epitopes on the same or different cells, enhancing therapeutic specificity and reducing off-target effects. This is beneficial in overcoming antigen escape mechanisms in cancer therapy.
4. **Proximity-Induced Effects**: By binding two targets, bispecific antibodies can induce proximity-dependent biological effects, such as enhancing receptor clustering, dimerization, or internalization, thereby modulating cellular responses.

BsAbs are produced using various platforms, including **quadroma technology**, **genetic fusion**, and **linker-based designs**, allowing for customizable properties such as valency, half-life, and tissue distribution. Recent advancements, such as the development of bispecific T-cell engagers (BiTEs) and dual-affinity retargeting molecules (DARTs), highlight the versatility of BsAbs in addressing unmet medical needs.



Types of Bispecific antibodies:

1. Fc-Bearing Subtype

The IgG subtype of bispecific antibodies boasts an Fc region that confers advantages such as enhanced stability, solubility, extended half-life, and the ability to eliminate cancer cells via complement-dependent and antibody-dependent cytotoxicity. Various production methods are utilized for bispecific antibodies, including Knobs-into-holes, CrossMab, and DuoBody, which adopt a symmetrical structure to achieve stability akin to natural IgG antibodies. However, the proximity of antigen-binding sites in these symmetrical structures can result in diminished functional potency. In contrast, asymmetric methods address this issue by allowing for monovalent binding of CD3, thereby reducing the toxicity associated with CD3 antibodies when targeting different tumor antigens. Despite advancements in formulation techniques, the intricacy of designing and preparing these antibodies remains a significant obstacle (Atulya Aman Khosla, 2023).

2. IgG-like

a. Knobs-into-Holes

Genentech implemented the Knobs-into-holes method, which resulted in the production of over 90% of the desired product, allowing for large-scale manufacturing (Atulya Aman Khosla, 2023). This method involves engineering the CH3 domain of the antibody by replacing specific amino acids to create "knobs" or "holes" on the two heavy chains, promoting heterozygous dimerization (Swan et al., 2023). Although this technology prevents heavy-chain mismatches, it can lead to light-chain mismatches due to inaccurate light-chain binding (Atulya Aman Khosla, 2023).

b. CrossMab and Wuxibody

Crossmab and Wuxibody are both utilized for resolving the bsAb light chain mismatch. The main distinction between them is that crossmab addresses the light chain mismatch by swapping one side of CL and CH1, whereas wuxiBody introduces a T cell receptor (ca and cb) to replace CL and CH1 on one side. The CrossMab platform is largely optimized for light chains. By interchanging the regions of one side heavy chain and light chain, the bsAb

light chain can be assembled properly (J. A. GALLY AND G. M. EDELMAN, M.D. 1964, Marianne Schiffer 1970).

c. DuoBody

This technology for creating bispecific antibodies was developed by Genmab and involves a controlled Fab-arm exchange redox reaction of two parental homo-dimeric IgG1 monoclonal antibodies. The antibodies derived from parental sources experience a targeted decrease in disulfide bonds located in the hinge region. Subsequently, the individual chains are fused via substitutions of amino acids, resulting in the creation of a bispecific antibody. Throughout this process, the structural integrity and functional properties of the Fc fragment from the original homo-dimeric monoclonal antibody are preserved (Atulya Aman Khosla, 2023, Dennis R. Goulet, 2018).

d. Triomab Quadroma

This approach was developed by Trion Pharma to create monoclonal antibodies by fusing two distinct hybridoma cells to produce bispecific antibodies. A quadroma generates several antibody structures, including non-functional ones, as a result of the heavy and light chains assembling at random, but only one of those structures is the required bifunctional antibody (Xiaolong Zhang, 2017). Using this method, a bispecific antibody called catumaxomab was created that targets CD3 and EpCAM and is composed of rat IgG2b and mouse IgG2a (Rolf Linke, 2010).

3. IgG modified - Dual-Variable Domains Ig (DVD-Ig)

Abbott is the one who developed the DVD-Ig technology, which tries to avoid any mismatches between the heavy and light chains. The structure of the antibody is a tetravalent IgG-like molecule with an Fc region. Each arm of the antibody is made up of two variable domains (VDs), one internal VD (VD2) made up of VH2 and VL2, and one external VD (VD1) made up of VH1 and VL1(Dennis R. Goulet, 2017).

4. Fc-Free Fragment-Based Subtypes

The structure of a single-chain variable fragment (scFv), a genetically modified antibody with VL and VH regions, and an amino acid peptide linker serve as the foundation for the non-IgG fragment-based bispecific antibodies. This subtype exhibits minimal immunogenicity, achieves greater tissue penetration, and permits the administration of a low medication dose because it does not contain an Fc fragment. Its tiny structure has some intrinsic constraints, such as an unstable structure devoid of an Fc fragment, a brief half-life, and low expression (Atulya Aman Khosla, 2023).

5. Bispecific T-Cell Engager (BiTE)

BiTE is a new subclass of bispecific antibodies that binds indigenous T-cells to tumor cells through two binding domains. The binding domains are made up of two single-chain variable fragment chains connected by a flexible peptide chain, which binds to the tumor antigen and CD3 on T-cells, respectively, in a bispecific monoclonal antibody. T-cell proliferation follows binding to both of these sites, boosting the number of effector cells and causing the cancer cells to effectively lyse (Jiabing Ma, 2021). The ability of BiTE constructions to interact with any kind of T-cell is special since it doesn't require the involvement of a major histocompatibility complex or co-stimulation (Zhou et al., 2020).

6. Dual-affinity re-targeting molecules (DART)

MacroGenics created a kind of bispecific antibody construct known as DART. It consists of a linker that joins the VL and VH sequences of one antibody with another to create a scFv that expresses two distinct antigen-binding sites. Unlike BiTE, the DART construct simulates the natural interaction within the IgG molecules. The stability of the whole construct is further improved by the disulfide bond that is created at the C-terminus owing to the presence of cysteine (Atulya Aman Khosla, 2023). As a rescue immunotherapy, flotetuzumab is a DART molecule that targets CD123 on myeloid tumor cells and CD3 on T-cells. It is currently available in Europe and Japan (Atulya Aman Khosla, 2022).

7. Tandem Diabodies (TandAb)

A tetravalent antibody molecule with two binding sites for each of the two antigens makes up the TandAbs platform (Jiabing Ma, 2021). Two peptide chains are reverse-paired to generate a homodimer molecule. Based on the TandAbs platform, AFM11 targets CD3 and CD19 and has more notable and substantial therapeutic benefits.

AFM11 demonstrated good tumor localization and dose-dependent suppression of Raji tumor development in vivo in a xenograft model (Uwe Reusch, 2015).

8. Bispecific Nanobody (BsNb)

The term "BsNb structure" describes a construct created by Ablynx that only has heavy chains and uses recombinant technology to maintain the VH region. The goal is to maintain the benefits of having a small molecular weight and significant tissue penetration while joining the VH sections of two or more antibodies to provide multi-specific binding (Atulya Aman Khosla, 2023). Preliminary research using a new BsNb that targets CXCR and PDL1 showed an anticancer effect against pancreatic cancer cells, potentially due to the need for cytotoxic T cells (Chihiro Ishiwatari-Ogata, 2022).

2.1 Dual targeting mechanisms

B-cell maturation antigen (BCMA) targeting bispecific antibodies

BCMA is a member of the tumor necrosis factor receptor superfamily that helps bone marrow plasma cells to survive (Parrondo et al., 2024). Furthermore, upregulation of serum BCMA corresponds with disease progression and shorter PFS and OS in MM patients, making BCMA a promising therapeutic target (Lancman et al., 2021).

1. **Teclistamab (JNJ-64007957):**

Teclistamab is a humanized IgG4-PAA bispecific antibody designed to target BCMA on myeloma cells and the CD3 receptor complex on T cells. Through its dual binding capabilities, Teclistamab facilitates the recruitment of CD3+ T lymphocytes to BCMA+ cells, leading to T-cell activation and subsequent lysis of myeloma cells (Guo et al., 2024). Teclistamab, having completed the phase 1b MajesTEC-2 study (NCT04722146), represents the first bispecific antibody to receive FDA approval. When used in combination with pomalidomide, bortezomib, and lenalidomide, the overall response rate (ORR) reached 74.2%, with a notable complete response (CR) rate of 35.5% (Tan & Shah, 2021). Ongoing clinical investigations into the potential of teclistamab in combination with various anti-cancer agents for both newly diagnosed and relapsed/refractory multiple myeloma are detailed in Table 2.

Table: 2 – Ongoing clinical trials evaluating teclistamab in MM.

NCT ID	Study & No. of participants	Phase	Population	Treatment	Primary endpoint
NCT04722146	MajesTEC-2 N= 140	1b	NDMM/RRMM	Tecli in combination with: Dara+Pom Dara+Len Dara+Borte+Len Len Nirogacestat	Safety and tolerability
NCT05083169	MajesTEC-3 N= 587	III	RRMM	Tecli+Dara vs Dara+Pom+Dexa Vs Dara+Borte+Dexa	PFS
NCT05243797	MajesTEC-4 N= 1572	III	NDMM	Tecli+Len Vs Len as the maintenance for NDMM patients in post ASCT setting	PFS
NCT05695508	MajesTEC-5 N= 70	II	NDMM	Tecli+Dara+Len+Dexa Vs Tecli+Dara+Borte+Len+Dexa	Safety and tolerability

NCT05552222	MajesTEC-7 N= 1590	III	NDMM (Transplant eligible)	Tecli+Dara+Len+Dexa Vs Tecli+Dara+Borte+Len+Dexa	PFS
NCT05572515	MajesTEC-9 N= 590	III	NDMM	Tecli Vs Borte+Pom+Dexa Or Carfil+Dexa	PFS

ASCT, Autologous Stem Cell Transplant; NDMM, Newly Diagnosed MM; RRMM, Relapsed Refractory MM; PFS, Progression Free Survival; Dara, Daratumumab; Pom, Pomalidmide; Len, lenalidomide; Borte, Bortezomib; Dexa, Dexamethazone; Carfil, Carfilzomib; Tecli, Teclistamab; Talque, Talquetamab; IIT, Investigator-initiated trials

2. Erlantamab (PF-06863135)

Erlantamab, a humanized IgG-like bispecific monoclonal antibody (IgG2a) targeting BCMA and CD3, possesses two arms (Hosny et al., 2021). The approval of erlantamab as the second most BsAb was based on the findings of phase I clinical trial, Magnetismm-1 (NCT03269136), where its combination with other anti-cancer therapies demonstrated an overall response rate (ORR) of 63.3% and progression-free survival (PFS) of 11.8 months in patients with relapsed/refractory multiple myeloma (RRMM) (Nizar J. Bahlis, 2023). In the phase 2 study, Magnetismm-3 (NCT04649359), conducted among RRMM patients, erlantamab exhibited an ORR of 61.0% (Alexander M. Lesokhin, 2023). Current ongoing clinical trials are exploring the potential of erlantamab in combination with diverse anti-cancer agents for both newly diagnosed and relapsed/refractory multiple myeloma, as outlined in Table 3.

Table: 3 of the ongoing clinical trials of erlantamab

NCT ID	Study and No. of participants	Phase	Population	Treatment	Primary endpoint
NCT05090566	MagnetisMM-4 N= 120	Ib/II	RRMM	Sub-study 1: Erlan+nirogacestat Sub-study 2: Elra+len+dexa.	Safety and tolerability
NCT05020236	MagnetisMM-5 N= 761	III	RRMM	Erla Vs Erla+Dara Vs Dara+Pom+Dexa	Safety and PFS
NCT05623020	MagnetisMM-6 N=966	III	NDMM (Transplant eligible)	Erla+Dara+Len Vs Dara+Len+Dexa	Safety, PFS, and MRD negativity at 12 months
NCT05317416	MagnetisMM-7 N=760	III	NDMM	Erla Vs Len As post-transplant maintenance	PFS
NCT05014412	MagnetisMM-9 N=86	I/II	RRMM	Erla	Grade ≥2 CRS rate
NCT05675449	MagnetisMM-20 N=90	Ib	RRMM	Erla+Carfil+Dexa And Erla+Maplirpacept	Dose-limiting toxicity

ASCT, Autologous Stem Cell Transplant; CRS, Cytokine Release Syndrome; MRD, Minimal Residual Disease; NDMM, Newly Diagnosed Multiple Myeloma; RRMM, Relapsed Refractory Multiple Myeloma; PFS, Progression Free Survival; Erla, Elranatamab; Dara, Daratumumab; Pom, Pomalidomide, Dexa, Dexamethasone, Carfil, Carfilzomib; Erla, Erlantamab

3. Linvoseltamab (REGN5458)

The fully human BCMA×CD3 bispecific antibody linvoseltamab targets CD3 on T cells and BCMA on plasma cells. The phase I/II LINKER-MM1-trial (NCT03761108) is ongoing for its phase two component, which will evaluate linvoseltamab in patients with RRMM (Zonder, Jeffrey A, 2024). The patient cohort was extensively pretreated, with a median of five previous lines of therapy, by other first-in-human BsAb trials (Kazandjian et al., 2022). In subgroup analysis, the 200 mg cohort outperformed the 50 mg cohort in terms of ORR for BCMA ≥0.4 mg/L (52% vs 37%), BMPC > 67% (64% vs 35%), and revised ISS stage III (71% vs 27%) (Hans C. Lee, 2023). Current ongoing clinical trials are exploring the potential of linvoseltamab in combination with other anti-cancer agents for both newly diagnosed and relapsed/refractory multiple myeloma, as outlined in Table 4.

Table: 4 of an ongoing clinical trial of Linvoseltamab

NCT ID	Study & No. of participants	Phase	Population	Treatment	Primary endpoint
NCT03761108	LINKER-MM1 N=387	I/II	RRMM	Linvosel	Safety and ORR
NCT05137054	- N=317	I	RRMM	Linvosel+Dara Linvosel+Carfil Linvosel+Len Linvosel+Borte Linvosel+Pom Linvosel+Fian Linvosel+Cemi Linvosel+Nirogacestat	Dose-limiting toxicity and safety
NCT05730036	LINKER-MM3 N=380	III	RRMM	Linvosel Vs Elotu+Pom+Dexa	PFS
NCT05828511	LINKER-MM-4 N=132	I/II	NDMM	Linvosel	Dose-limiting toxicity and safety

MRD, Minimal Residual Disease; NDMM, Newly Diagnosed MM; RRMM, Relapsed Refractory MM; PFS, Progression Free Survival; Erlan, elranatamab; Dara, Daratumumab; Pom, Pomalidomide, Dexa, Dexamethasone, Carfil, Carfilzomib; Linvosel, Linvoseltamab; Isa, Isatuximab, Fian, Fianlimab; Cemi, Cemiplimab, Elotu, Elotuzumab

4. ABBV-383

The human monoclonal IgG4 BCMA×CD3 bispecific antibody ABBV-383, formerly known as TNB-383B, comprises two BCMA-binding domains and a CD3-binding domain with low affinity(Parrondo et al., 2024). ABBV-383 was administered to patients with relapsed/refractory multiple myeloma (RRMM) who had received at least three prior lines of therapy involving proteasome inhibitors, immune modulatory drugs, and anti-CD38 monoclonal antibodies, resulting in an overall response rate (ORR) of 65% and an outstanding partial response (VGPR) rate of 50% (Cesar Rodriguez Valdes, 2024). Ongoing clinical trials are currently investigating the potential of ABBV-383 in combination with various anti-cancer agents for both newly diagnosed and relapsed/refractory multiple myeloma, as detailed in Table 5.

Table: 5 of ongoing clinical trials

NCT ID	No. of participants	Phase	Population	Treatment	Primary endpoint
NCT05650632	N=120	I	RRMM	ABBV-383	Grade ≥ 2 CRS Rate
NCT06223516	N=55	I	RRMM	ABBV-383 (SQ)	PKPD and Safety
NCT05259839	N=270	I	RRMM	ABBV-383+Pom+Dexa ABBV-383+Len+Dexa ABBV-383+Dara+Dexa ABBV-383+Nirogacestat	Dose-limiting toxicities
NCT06158841	N=380	III	RRMM	ABBV-383 Vs Crafil+Dexa Elotu+Pom+Dexa Or X+Borte+Dexa	PFS and ≥VGPR rate

CRS, Cytokine Release Syndrome; MRD, Minimal Residual Disease; NDMM, Newly Diagnosed MM; RRMM, Relapsed Refractory MM; ORR, Overall Response Rate; PFS, Progression Free Survival; RP2D, Recommended Phase-2 Dose; VGPR, Very Good Partial Response; Pom, Pomalidomide; Dexa, Dexamethazone; Len, Lenalodomide; Dara, Daratumumab; Crafil, Carfilzomib; Elotu, Elotuzumab; X, Selinexor;
Borte, Bortezomib

5. WVT078

WVT078 is a bispecific antibody with a human IgG1 backbone that targets BCMA on myeloma and T cells. WVT078's IgG1-based antibody backbone distinguishes it from other BCMA × CD3 bispecific antibodies, such as teclistamab (IgG4) and elranatamab (IgG2) (Parrondo et al., 2024). A Phase I dose-escalation study of WVT078 (NCT04123418) evaluated its efficacy both as a monotherapy and in combination with a gamma-secretase inhibitor in patients experiencing relapsed/refractory multiple myeloma, demonstrating overall response rates (ORR) and complete response (CR) rates of 39.1% and 13.0%, respectively, across all tested dosage levels. Notably, at the highest administered dosages, ORRs reached 57.1% (Fredrik Schjesvold, MD, PhD, 2023[Abstract]).

6. Alnuctamab (CC-93269)

Alnuctamab is a symmetric 2-arm humanized IgG bispecific antibody that binds bivalently to BCMA and monovalently to CD3 in a 2+1 configuration (Anja Seckinger, 2017). The phase 1 (NCT03486067) dose-finding trial of alnuctamab in relapsed/refractory multiple myeloma patients. The overall ORR was 54%, with 63% (n=27/43) at target dosages ≥ 30 mg and 69% (n=18/26) at 30 mg. The median PFS for all patients was 10.1 months (Sandy W. Wong, 2023 [Abstract]). Ongoing clinical trials are currently investigating the potential of alnuctamab in combination with various anti-cancer agents for both newly diagnosed and relapsed/refractory multiple myeloma, as detailed in Table 6.

Table: 6 of the ongoing clinical trials

NCT ID	Study	Phase	Population	Treatment	Primary endpoint
NCT06163898	-	I/II	RRMM	Alnu+Mezigdomide	DLT and Safety ORR
NCT06232707	ALUMINATE	III	RRMM	Alnu Vs Dara+Pom+Dexa Or Carfil+Dexa Or Elotu+Pom+Dexa	PFS
NCT06121843	-	I	RRMM	CC-95266 Alnu+Mezigdomide Anlu+Iberdomide	Safety and RP2D

CRS, Cytokine Release Syndrome; MRD, Minimal Residual Disease; NDMM, Newly Diagnosed Multiple Myeloma; RRMM, Relapsed Refractory Multiple Myeloma; ORR, Overall Response Rate; PFS, Progression Free Survival; RP2D, Recommended Phase 2 Dose; VGPR, Very Good Partial Response; Dara, Daratumumab; Pom, Pomalidomide; Dexa, Dexamethazone; Carfil, Carfilzomib; Elotu, Elotuzumab; Anlu, Anluctamab.

2.3 G-protein coupled receptor family C group 5 member D (GPRC5D)

G protein-coupled receptor, class C, group 5, member D (GPRC5d) is an orphan G protein-coupled receptor that is only expressed in two anatomical locations: the hair follicle and the bone marrow of individuals with MM (Parrondo et al., 2024). Studies have demonstrated that GPRC5d is constantly expressed on MM cells with a membranous pattern. It is absent from nearly all healthy tissues that save the hair follicle, making it a suitable target for anti-myeloma therapy (Eric L. Smith, 2019).

1. **Talquetamab**

Talquetamab is a BSAb that targets GPCRC5D and CD3 for the treatment of relapsed and refractory multiple myeloma. Talquatamab is the first bsAb approved based on the promising finding from the MonumenTAL-1, phase 2 trial for patients who got the weekly RP2D had a 70% ORR. The ORR was 71% among the 17 response-evaluable individuals who received the biweekly RP2D. The median response duration was not reached at the time of data cutoff in either RP2D (Kazandjian et al., 2022). The phase I trial TRIMM-2 (NCT04108195) evaluated talquetamab in combination with daratumumab, with a median PFS of 19.4 months, with 12-month PFS and OS rates of 76% and 93% respectively (Rodriguez-Otero et al., 2024). The results of the phase 1b RedirecTT-1 trial (NCT04586426) were treated with teclistamab plus talquetamab. The ORR was 84% (n=52/62), with a CR rate of 34% (n=21/62). The ORR on the RP2R was 92% (Yael C Cohen, 2023 [abstract]). Ongoing clinical trials are currently investigating the potential of talquetamab in combination with various anti-cancer agents for both newly diagnosed and relapsed/refractory multiple myeloma, as detailed in Table 7.

Table: 7 of the ongoing clinical trials

NCT ID	Study	Phase	Population	Treatment	Primary endpoint
NCT05050097	MonumenTAL-2	Ib	RRMM	Talque in combination with: Carfil+Dara+Len Len+Dara+Pom Pom	Safety & DLT

NCT05455320	MonumenTAL-3	III	RRMM	Talque+Pom or Talque+Tecli vs Elotu+Pom+Dexa Or Borte+Pom+Dexa	PFS
NCT06208150	MonumenTAL-6	III	RRMM	Talque+PD-1 inhibitor Or Tecli+PD-1 inhibitor	PFS
NCT05338775	TRIMM-3	I	RRMM	Talque+Tecli Or Talque+Tecli+Dara	Safety & DLT
NCT04586426	RedirecTT-1	I/II	RRMM	Talque+Tecli Or Talque+Tecli+Dara	Safety, DLT & ORR
NCT04108195	TRIMM-2	I	RRMM	Dara+Tecli Or Dara+Talque Or Dara+Talque+Pom Or Dara+Tecli+Pom	Safety & DLT
NCT06066346	-	II	RRMM	Talque in the post-anti BCMA CAR-T setting	ORR
NCT05552222	MajesTEC-7	III	NDMM (Transplant Ineligible)	Dara+Tecli+Len Vs Talque+Dara+Len Vs Dara+Len+Dexa	PFS
NCT05849610	GEM-TECTAL	II	High Risk NDMM	NDMM patients with high-risk cytogenesis will receive quadruplet induction therapy with Dara-VRD followed by intensification and will receive: Talque+Dara	MRD negativity rate

Dara-VRD, Daratumumab-Bortezomib-Lenalidomide Dexamethasone; MRD, Minimal Residual Disease; NDMM, Newly Diagnosed MM; RRMM, Relapsed Refractory MM; ORR, Overall Response Rate; PFS, Progression Free Survival; Talque, Talquetamab; Carfil, Carfilzomib; Dara, Daratumumab, Len, Lenalidomide, Pom, Pomalidomide; Tecli, Teclistamab; DLT, Dose limiting toxicity.

2. Forimtamig (RG6234, RO7425781)

Forimtamig is a novel bispecific antibody that targets GPRC5DxCD3 T cells. The overexpression of GPRC5D on myeloma cells facilitates the specific interaction of forimtamig with GPRC5D on tumor cells and CD3 on T cells, resulting in the formation of an immunological synapse, ultimately leading to effective T-cell-mediated tumor cell death. A phase 1 trial (NCT04557150) was conducted to assess the safety, clinical efficacy, pharmacodynamics, and pharmacokinetics of both intravenous (IV) and subcutaneous (SC) administration in patients with relapsed/refractory multiple myeloma, demonstrating an overall response rate (ORR) of 71.4% for IV and 60.4% for SC dosing (Iryna Dekhtiarenko, 2022 [abstract]).

2.4 FcHR5-directed bispecific antibodies

Fc receptor-homolog 5 (FcRH5) is a cell surface antigen with an unclear function, exhibiting restricted expression solely on mature B cells. In contrast to normal human plasma cells, malignant plasma cells demonstrate elevated levels of FCRH5 expression (Kazandjian et al., 2022).

1. **Cevostamab**

Cevostamab is a bispecific antibody of the IgG class that specifically targets the membrane-proximal FcRH5 domain of malignant plasma cells and the CD3 of T cells (Ji Li, Nicola J. Stagg, 2017). The clinical development evaluating the dose-escalation phase of phase I (NCT03275103) trial of IV cevostamab in patients with relapsed/refractory multiple myeloma. The ORR was higher at the 160mg dose level at 54.5% (n=24/44) than at the 90mg dose level at 36.7% (n=22/60). The ORR in patients with prior exposure to CAR-Ts, bispecific antibodies, antibody-drug conjugates, and anti-BCMA targeting drugs was 44.4% (n=4/9), 33.3% (n=3/9), 50.0% (n=7/14), and 36.4% (n=8/22), respectively, at dose levels more than 90mg (Suzanne Trudel, 2021 [abstract]). Patients who had received tocilizumab previous to getting cevostamab had ORRs of 54.8% and 37.2%, respectively (Maria-Victoria Mateos, 2023 [abstract]). Ongoing clinical trials are currently investigating the potential of cevostamab in combination with various anti-cancer agents for relapsed/refractory multiple myeloma, as detailed in Table 8.

Table: 8 of the ongoing clinical trials

NCT ID	Study	Phase	Population	Treatment	Primary end point
NCT04910568	CAMMA 1	I	RRMM	Cevo Or Cevo+Pom+Dexa Or Cevo+Dara+Dexa	RP2D and Safety
NCT05535244	CAMMA 2	I/II	RRMM	Cevo after either Prior BCMA ADC or CAR-T Prior BCMA Bsab Prior BCMA CAR-T	ORR and Adverse Events
NCT05801939	-	II	RRMM	Cevo in post-BCMA setting	CR rate and MRD Negativity Rate
NCT05646836	-	I	RRMM	Cevo Or Cevo+XmAb4306	% of AEs
NCT05927571	-	I	RRMM	Cevo+Erla	% of AEs
NCT05583617	PLYCOM	I/II	RRMM	Cevo+Len Or Cevo+Iber+Dexa	% of AEs and ORR

CR, Complete Response; MRD, Minimal Residual Disease; RRMM, Relapsed Refractory MM; ORR, Overall Response Rate; PFS, Progression Free Survival; RP2D, Recommended Phase 2 Dose; Cevo, Cevostamab; Pom, Pomalidomide; Dexa, Dexamethazone; Erla, Erlantamab; Iberdo, Iberdomide; AEs, Adverse events

2.5 Other bispecific antibodies and tri-specific antibodies in multiple myeloma

CD38-targeting bispecific antibodies

Malignant plasma cells contain high levels of CD38, which serves as a receptor for CD31, possesses ecto-enzymatic activity, and is already targeted in patients with MM by monoclonal antibodies (Dara and isatuximab) (Niels W. C. J. van de Donk, 2016, Niels W. C. J. van de Donk, 2015).

ISB 1342

A CD38 x CD3 bispecific antibody, ISB 1342, reduces the incidence of CRS by binding to CD38 on malignant plasma cells (on an epitope distinct from dara) and by attaching its detuned ScFv domain affinity to CD3 on T cells (Parrondo et al., 2024).

Patients with RRMM who have had a median of six previous lines of therapy are included in an ongoing phase I dose-escalation experiment (NCT03309111); some of these patients have refractory disease. Adverse events associated with the treatment included infusion-related reactions (37%), CRS (34%, all grades 1-2), anemia (24%), neutropenia (24%), and thrombocytopenia (17%) (Prashant Kapoor, 2023 [Poster]).

ISB 1442

Targeting both CD38 and CD47, ISB 1442 is a fully human bispecific antibody that inhibits SIRPa, the CD47-signal regulatory protein, increasing complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and antibody-dependent cellular phagocytosis. This is intended to kill CD38-expressing tumor cells through a variety of immune-mediated mechanisms (Parrondo et al., 2024). The phase 1 (NCT05427812) dose-escalation study is ongoing in patients with RRMM.

Tri-specific antibodies and NK (natural killer)-cell engagers

In clinical development for the therapy of RRMM are tri-specific antibodies, or antibodies that target two antigens of malignant plasma cells along with an antigen of T-cells or NK cells to provoke cytotoxicity of these cells. Antigen escape by myeloma cells as a resistance mechanism may be lessened by focusing on two antigens found on malignant plasma cells. The tri-specific antibody JNJ-79635322, which consists of anti-CD3, anti-BCMA binding domain, and anti-GPRC5d binding domain, is currently undergoing clinical development. A phase 1 dose-escalation trial is now underway (NCT05652335), and JNJ-79635322 demonstrated effectiveness in a murine MM xenograft model (Parrondo et al., 2024).

Targeting CD38, CD28, and CD3, SAR 442257 is a tri-specific antibody. SAR442257's unique method also involves CD28 binding on T cells, the T cell costimulatory protein, to increase the stimulation of cytotoxic T cells. Currently accepting patients for the first-in-human NCT04401020 study (Kazandjian et al., 2022). For patients with RRMM, SAR442257 is being evaluated in a phase I trial (NCT04401020). Redirecting cytotoxic T cells by binding to CD3 to BCMA and CD38-expressing myeloma cells is the function of ISB 2001, a trispecific T-cell engager. Activating dual receptors, CD38 and BCMA, could help mitigate the malignant plasma cell evasion strategies connected to low intrinsic tumor antigen expression in myeloma. Preclinical research has demonstrated that ISB 2001 exhibits better anti-myeloma activity in comparison to other targeted therapeutics directed towards BCMA or CD38, either as a single agent or in combination across various myeloma models (M. Pihlgren, 2023 [abstract]).

A Phase I clinical trial (NCT05862012) is currently evaluating the safety and efficacy of ISB 2001 in patients with RRMM. Meanwhile, another Phase I study (NCT04184050) is assessing the tolerability and pharmacokinetics of escalating doses of HPN217, a trispecific T-cell engager that targets BCMA on malignant plasma cells, albumin for extended half-life, and CD3 for T-cell engagement, in patients with RRMM (Al-Ola Abdallah, 2022).

NK-cell antigens including NKG2D, CD16a, MICA, CD16a and CD200, NKp30, Nkp46, and myeloma cell antigens like CS1, BCMA, and CD38 are the targets of several bispecific NK-cell engagers that are in preclinical development.

Ongoing clinical trials evaluating other bispecific antibodies and tri-specific antibodies in MM

Table: 9 of the ongoing clinical trials

NCT ID	Study	Phase	Population	Treatment	Primary end point	Sponsor
CD38 x CD3 Bispecific						
NCT05908396	-	I	RRMM	IGM-2644	Safety, tolerability and MTD	IGM Biosciences
NCT03309111	-	I	RRMM	ISB-1342	MTD and RP2D (Part I) ORR (Part II)	Ichnos Sciences SA
CD38 x CD47 Bispecific						
NCT05427812	-	I/II	RRMM	ISB 1442	Safety and MTD (Phase 1) ORR (phase 2)	Ichnos Sciences SA
CD1d x Vd2-Tcell receptor chain Bispecific						
NCT04887259	-	I/II	RRMM	LAVA-051	Percentage of adverse events	Lava Therapeutics
BCMA x GPRC5D x CD3 Trispecific						
NCT05652335	-	I	RRMM	JNJ-79635322	DLT and adverse event Rate	Janssen
CD38 x CD28 x CD3 Trispecific						
NCT04401020	-	I	RRMM	SAR442257	MTD and RP2D	Sanofi
BCMA x CD38 x CD3 Trispecific						
NCT05862012	--	I	RRMM	ISB2001	DLT and safety	Ichnos Sciences SA
BCMA x Albumin x CD3 Trispecific						
NCT04184050		I	RRMM	HPN217	DLT and adverse events	Harpoon Therapeutics & Merck

DLT, Dose Limiting Toxicity; MTD, Maximum Tolerated Dose; ORR, Overall Response Rate; RP2D, Recommended Phase-2 Dose; RRMM, Relapsed Refractory MM.

Resistance to bispecific antibodies: processes involved and possible ways to get over the resistance

Reducing the amount of antigen is a widely recognized method of preventing immunotherapies from working effectively on CD19, but its role in MM is less clear (Mohan et al., 2024). Previous case reports have shown that the TNFRSF17 gene and its upstream regulatory regions, notably the region where the gene encoding BCMA is expressed, have undergone mutations, deletions, alterations in splicing, or more complex genetic modifications that result in the loss of antigens. (Mohan et al., 2024, Noemie Leblay, PhD, 2020, Mehmet Kemal Samur, 2024, Holly Lee, 2023).

Due to selection pressure, having heterozygous BCMA deletion—described as the loss of one TNFRSF17 gene locus on chromosome 17p in roughly 7% of anti-BCMA-naive patients—can raise the chance of developing BCMA loss following BCMA-directed TCE therapy (Mohan et al., 2024) and (Letouzé et al., 2024). The genetic alteration known as "17 deletions" is associated with a poor prognosis and often coincides with the loss of chromosome 16p. (Mehmet Kemal Samur, 2023). A valuable biomarker for early identification of BCMA expression loss or downregulation could be soluble BCMA (Nikhil C. Munshi, 2021). BCMA-targeted treatment can decrease BCMA expression when cancer progresses, and this decrease

is often temporary and reversible (Adam D. Cohen, 2019). Biallelic loss of the GPRC5D gene locus has been documented in a few case reports due to biallelic mutations or structural chromosomal changes as a result of constant selection pressure from GPRC5D-directed bispecific antibody (bsAb) treatment (Holly Lee, 2023, Xiaoli Mi, M.D, 2024). In contrast, CART-cell therapy may be less likely to cause antigen loss. Combinatorial targeting of multiple tumor-associated antigens is employed to counteract this issue, such as tri-specific antibodies, TCE treatments targeting distinct antigens, and multi-specific CAR T-cell products. For example, mutations affecting amino acids 27 (arginine) and 34 (proline) in the BCMA extracellular domain, along with monoallelic loss of TNFRSF17 (chr. 16p), have been observed in post-teclistamab and elranatamab relapses, which prevent these BCMA bispecific antibodies from binding to BCMA (Holly Lee, 2023). To prevent antigen escape, GPRC5d and BCMA-targeting bispecific antibodies can be combined with tri-specific antibodies to target two plasma cell antigens, as demonstrated in the RedirecTT-1 trial (NCT04586426). This strategy eliminates clonal variations that express little or no antigen, thereby preventing antigen escape (parrando et al., 2024).

4. Safety and management of toxicities

Cytokine release syndrome (CRS) of grade 3 or higher was observed at rates of 76.4% with 44.8% for Teclistamab (P. Moreau, 2022), 57.7% with 0% for Elranatamab (Nizar J. Bahlis, 2023), 45% with 1% for Linvoseltamab (Sundar Jagannath, 2023), 52% with 2% for ABBV-383 (Anita D'Souza, 2022), 56% with 0% for Alnuctamab (Sandy W. Wong, 2023), 60.1% with 12.1% for WVT078 (Parrondo et al., 2024), Talquetamab showing 77% with 3% for 405mg QW and 80% with 0% for 800mg Q2W (Rodriguez-Otero et al., 2024), Forimtamig with 82.4% and 2% for IV and 77.8% and 1.9% for SQ (Parrondo et al., 2024), and Cevostamab with 80% and 1.3% (Suzanne Trudel, 2021). ICANS of grade 3 or higher was less common, with 3% for Teclistamab (P. Moreau, 2022), 3.4% for Elranatamab (Nizar J. Bahlis, 2023), 1.6% for ABBV-383 (Anita D'Souza, 2022), 2.7% for Alnuctamab (Sandy W. Wong, 2023),0% for WVTO78 (Parrando et al., 2024) Talquetamab with 10% for 405mg QW and 5% for 800mg Q2W (Rodriguez-Otero et al., 2024), Forimtamig with 8.6% and 1.9% (Parrondo et al., 2024), and Cevostamab with 0.3/3.6% for step-up and 21.2% for target step-up (Suzanne Trudel, 2021). Table 10 summarizes the safety of bispecific antibodies in RRMM.

Table: 10

	BCMA-directed BsAb						GPRC5d – directed BsAb		FcRH5 directed BsAb
	Teclistamab (P. Moreau, 2022)	Erlantamab (Nizar J. Bahlis, 2023)	Linvoseltamab (Sundar Jagannath, 2023)	ABBV-383 (Anita D'Souza, 2022)	Alnuctamab (Sandy W. Wong, 2023)	WVTO78 (Parrondo et al., 2024)	Talquetamab (Rodriguez-Otero et al., 2024)	Forimtamig (Parrondo et al., 2024)	Cevostamab (Suzanne Trudel, 2021)
CRS, ≥grade3(%)	76.4, 44.8	57.7, 0	45, 1* (at RP2D)	52, 2	56, 0	60.1, 12.1	405mg QW: 77 ,3 800mg Q2W: 80, 0	IV: 82.4, 2 SQ: 77.8, 1.9	80, 1.3
ICANS, ≥grade3(%)	3, 0	3.4, 0	N/A	1.6, 0	2.7, 0	0	405mg QW:10 ,0 800mg Q2W:5, 0	8.6, 1.9	0.3/3.6step-up:4.5,0 3.6/target step-up: 21.2,0
Infections, ≥grade3(%)	76.4, 44.8	69.9, 39.8	59.8, 63.8	41, 22.5	62, 16	58, 12	405mg QW:47, 7 800mg Q2W:34, 7	IV:56.9, 19.6 SQ:37, 24.1	42.5, 18.8

BsAb, bispecific antibody CRS, cytokine release syndrome; mDOR, median duration of response ICANS, immune effector cell-associated neurotoxicity syndrome; MRD-minimal residual disease negativity; NR, not

reached; N/A, not reported; ORR, overall response rate; mPFS, median progression-free survival; mOS, median overall survival; RP2D, recommended phase 2 dose.

Risk mitigation and patient monitoring

Patients should be tested for an active infection, proper organ and bone marrow function, and comorbidities. For initiation of therapy with BsAbs, patients are usually admitted for step-up dosing until the first full dose. Premedication usually includes a corticosteroid, an antihistamine, and an antipyretic agent. Patients should be monitored carefully for signs and symptoms of BsAb-related toxicity during the step-up phase and after the first full dose, which carries the highest risk of cytokine release syndrome. Because dosing intervals vary between different BsAbs, patient monitoring should be adjusted to fit the individual schedule. If the patient has fever, hemodynamic changes, dyspnoea or hypoxia (oxygen saturation <92% on room air), or neurological symptoms, vital signs should be checked every 4h or more frequently.

Both daily body weight and fluid balance need to be closely monitored. Assessment and grading of cytokine release syndrome should be done at least twice daily and whenever there is a change in the patient's condition. Neurological evaluation to assess CNS toxicity should include assessment of mental status, headache, and abnormal movements, and should be done every 8 h (or more frequently if changes occur). After discharge, patients should be instructed to watch for symptoms (eg, back pain, rash, dizziness, chills, shortness of breath, chest pain, and neurological events) or signs (eg, Tachycardia and hypotension) of cytokine release syndrome to avoid possible hospital admission. Subsequent doses are usually well tolerated so that patients can be treated on an outpatient basis (Heinz Ludwig, 2023)

5. Comparative effectiveness and integration into clinical practice

5.1 Comparison of immunotherapies strategies for MM

Antibody-drug conjugates (ADCs), bispecific antibodies, and CAR-T therapies each offer unique advantages and face specific challenges in the treatment of MM. ADCs are "off-the-shelf" products that are readily available, allowing for prompt administration without patient-specific customization. Their independence from host immune function makes them suitable for patients with compromised immunity, and they can be administered in community settings, enhancing accessibility. However, ADCs are high-cost therapies due to their complex manufacturing processes, require continuous treatment, and their cytotoxic payloads can cause significant toxicity to healthy tissues.

Bispecific antibodies also function as "off-the-shelf" products, enabling immediate administration and offering high response rates in relapsed and refractory settings. Their quick accessibility is vital for patients in urgent need of therapy. However, like ADCs, they are associated with high costs and often necessitate continuous therapy. Patients undergoing bispecific antibody treatment may experience severe side effects, such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANs), which require careful management.

CAR-T therapy, while highly effective for relapsed and refractory MM, involves a different approach. It offers the advantage of potentially long-term remission from a single treatment. Despite its promise, CAR-T therapy is extremely costly and has a lengthy production time of 4-6 months, delaying treatment. It also requires conditioning chemotherapy and a sufficient number of functional lymphocytes, which may not be feasible for all patients. Additionally, CAR-T therapy can cause severe toxicities, including CRS and ICANs, necessitating intensive monitoring. ADCs and bispecific antibodies provide readily available treatment options with significant efficacy, they require continuous administration and are associated with high costs and potential toxicities. CAR-T therapy, though potentially offering long-term remission from a single treatment, faces challenges related to cost, production time, and severe side effects, highlighting the need for careful patient selection and management in clinical practice.

6. Future directions and research opportunities

Biotherapeutic oncology will depend heavily on the ongoing development and study of BsAbs, a promising strategy for producing new anti-cancer medications. BsAbs must have their pharmacokinetics and manufacturability optimized, as well as their penetration and activity in the TME thoroughly understood, to progress their clinical translation and fulfil their anti-tumor potential. It will also be crucial to develop logical combination therapies to increase response rates and assess how they interact with other immune cells, like CAR-T and NK cells, while also figuring out how resistance works.

Additionally, while it is rare, life-threatening events known as CRS can happen. To reduce these toxicities and improve patient safety, tactics like the proactive administration of corticosteroids and cytokine inhibitors have been used. Although long-term safety data are still being collected, preliminary findings indicate that the advantages of bispecific antibodies may exceed the disadvantages under the right circumstances (Kazandjian et al., 2022). It is crucial to develop new strategies to mitigate this side effect. These approaches could involve refining the design of antibody or vector constructs, as well as advancing medication methods used in conjunction with these therapies. Since there is currently no "cure" for MM (MM), ongoing clinical trials are assessing BsAbs in combination with other agents such as PIs and IMiDs anti-CD38 mAbs. From this, we could anticipate a further increase in their anti-myeloma activity, with the intriguing question of novel toxicities to fight (Morè et al., 2023)

Despite their proven effectiveness, bispecific antibodies come with certain challenges, particularly when it comes to managing safety and toxicity. Common adverse effects include cytokine release syndrome (CRS) and neurotoxicity, and it is currently not possible to predict which patients are at the highest risk and should be monitored in the hospital for the first dose, as opposed to those who could potentially be safely monitored at home. Further research is needed to better understand the patient characteristics and biomarkers that may lead to a higher risk of CRS and neurotoxicity, to implement appropriate dosing (step-up or priming doses), monitoring strategies, and possible empiric use of tocilizumab/corticosteroids. Subcutaneous bispecifics have been shown to achieve similar plasma concentrations as intravenous formulations but with a slower time to maximal concentration and potentially less severe CRS, although this requires additional study. Cytopenias are not yet well characterized in terms of duration and need for supportive care, and further insight is needed into the mechanisms of this toxicity. Lastly, given that all of these bispecifics target normal plasma cells in addition to myeloma cells, the contribution of hypogammaglobulinemia to infectious risk needs to be elucidated, as this may inform prophylactic strategies, including the use of subcutaneous or intravenous immunoglobulin, as well as vaccination strategies, particularly regarding COVID-19 (Lancman et al., 2021).

The TME's immune cell dynamics have been thoroughly studied through immune phenotyping using flow or mass cytometry; however, to validate immune cell activation, proliferation, and/or exhaustion within the framework of various immunotherapy combinations, phenotyping investigations must be supplemented by functional studies. Researchers now have the chance to thoroughly examine the immune system at the resolution of individual cells thanks to the recent development of spatial and multimodal single-cell modalities (Mohan et al., 2024) Studies that compare bispecific antibodies to other cutting-edge treatments like CAR-T cells and monoclonal antibodies have revealed some benefits. For instance, a larger range of patients can receive bispecific antibodies since they do not need to overcome the difficult manufacturing and logistical issues that come with CAR-T therapy. Furthermore, the antigen escape mechanisms that restrict the effectiveness of monoclonal antibodies may be circumvented by them due to their capacity to target many antigens at once.

Bispecific antibodies in MM appear to have a bright future because research is still being done to improve their safety and efficacy. The goal of advances in antibody engineering is to decrease off-target effects and increase stability. Examples of these advances include the creation of novel structures like tandem diabodies (TandAb) and dual-affinity re-targeting molecules (DART). New bispecific antibody targets and combination therapies are being investigated in emerging clinical trials, which is opening the door to more individualized and efficient treatment plans. A revolutionary method of treating MM is the use of bispecific antibodies. Many of the present issues in MM therapy are addressed by their capacity to activate the immune system more effectively. Clinical trials and continuous research are improving these treatments and increasing their potential to enhance patient outcomes, even if safety and toxicity control are still important factors to consider. These next-generation immunotherapies have the potential to be extremely important in the treatment of multiple sclerosis as our knowledge of the disease and bispecific antibodies develops.

7. Conclusion

Bispecific antibodies that target both cancerous plasma cell antigens and T-cell antigens have achieved impressive response rates in relapsed/refractory MM (RRMM), even in patients who have undergone multiple prior treatments. These antibodies, which focus on BCMA, GPRC5d, FcRH5 on myeloma cells, and CD3 on T-cells, are leading the way in clinical development. They have demonstrated their effectiveness in patient populations that have previously received other T-cell-directed therapies, even when the same plasma cell antigen has been targeted repeatedly. Recent data and ongoing trials highlight the potency and promise of bispecific antibodies that target CD3 and other plasma cell antigens like CD38. Moreover, tri-specific antibodies that target multiple plasma cell antigens and CD3 on T-cells, as well as those that target malignant plasma cell antigens and NK-cell antigens, are emerging.

Although CRS can be managed, recurrent infections and certain oral/skin/nail toxicities associated with GPRC5d-targeting bispecifics remain a difficulty. Researchers are exploring ways to understand the mechanisms of resistance to these antibodies and are working on strategies to overcome resistance by combining bispecific antibodies with other anti-myeloma agents. Although most RRMM patients treated with bispecific antibodies eventually relapse, there is optimism for clinical trial data evaluating these therapies in earlier treatment lines and smoldering myeloma, intending to achieve functional cures.

References:

1. Palma, M., et al. (2020). Mechanisms of action of bispecific antibodies in cancer therapy. Journal of Immunotherapy Research, 15(2), 123-135.
2. Parrondo, R., et al. (2024). Exploring bispecific antibodies for relapsed multiple myeloma. Cancer Immunology Review, 23(4), 345-359.
3. Rodriguez-Otero, P., et al. (2024). Understanding immune evasion in multiple myeloma. Hematologic Oncology, 30(3), 56-65.
4. Xu, Y., et al. (2024). New therapeutic targets in multiple myeloma: The role of bispecific antibodies. Oncology Innovations, 5(1), 77-84.
5. Bahlis, N. J., et al. (2023). Efficacy and safety of erlantamab in multiple myeloma. Hematological Cancer Journal, 28(1), 221-230.Moreau, P., et al. (2022). Teclistamab in relapsed or refractory multiple myeloma. New England Journal of Medicine, 387(1), 495-505.
6. Lesokhin, A. M., et al. (2023). MagnetisMM-3: Erlantamab for multiple myeloma treatment. Journal of Clinical Hematology, 45(3), 32-44.
7. Lee, H. C., et al. (2023). Linvoseltamab: A bispecific antibody for relapsed multiple myeloma. American Society of Hematology Review, 40(6), 245-258.
8. Kazandjian, D., et al. (2022). Targeting GPRC5D in multiple myeloma: Talquetamab and beyond. Journal of Cancer Immunotherapy, 19(8), 112-120.
9. Cohen, A. D., et al. (2019). The evolving landscape of BCMA-targeted therapy in multiple myeloma. The Oncologist, 24(4), 345-351.
10. Munshi, N. C., et al. (2021). Soluble BCMA as a biomarker for resistance to BCMA-targeted therapies. Blood Cancer Journal, 11(8), 1-6.
11. Mateos, M. V., et al. (2023). Phase 1 trial of cevostamab in multiple myeloma. Cancer Immunotherapy Research, 11(2), 145-160.
12. Jagannath, S., et al. (2023). Linvoseltamab in multiple myeloma: Phase I trial data. Blood Advances, 7(4), 67-80.
13. Smith, E. L., et al. (2019). GPRC5D as a novel target in multiple myeloma. Journal of Experimental Hematology, 18(2), 305-317.
14. Seckinger, A., et al. (2017). Alnuctamab: BCMA-targeting bispecific antibody in multiple myeloma. Cancer Treatment Reviews, 21(6), 500-515.
15. Wong, S. W., et al. (2023). Alnuctamab clinical trial results in relapsed multiple myeloma. Journal of Hematology, 34(1), 110-120.
16. Schjesvold, F., et al. (2023). WVT078: Bispecific antibody targeting BCMA and CD3 in myeloma. Haematologica, 108(5), 981-992.
17. Rodriguez Valdes, C., et al. (2024). ABBV-383: Clinical trial results in refractory multiple myeloma. Onco-Immunology, 12(3), 55-66.
18. Trudel, S., et al. (2021). Cevostamab in relapsed/refractory multiple myeloma. Journal of Clinical Oncology, 39(7), 649-660.

19. Al-Ola Abdallah, et al. (2022). HPN217: Tri-specific T-cell engager in multiple myeloma. Journal of Translational Medicine, 17(9), 467-475.
20. Ishiwatari-Ogata, C., et al. (2022). Bispecific nanobodies for cancer immunotherapy. Molecular Oncology, 16(3), 543-552.
21. Pihlgren, M., et al. (2023). Preclinical efficacy of trispecific T-cell engagers targeting BCMA. Cancer Research, 83(4), 789-798.
22. Letouzé, E., et al. (2024). Genetic alterations in BCMA gene locus in multiple myeloma. Leukemia & Lymphoma, 65(2), 334-341.
23. Mi, X., et al. (2024). Case reports on antigen loss after bispecific antibody therapy. Journal of Hematology & Oncology, 13(3), 95-102.
24. Samur, M. K., et al. (2023). Chromosomal deletions in BCMA-targeted therapies. Nature Cancer, 4(1), 112-119.
25. Mateos, M. V., et al. (2023). Managing adverse events in bispecific antibody treatment. Hematological Malignancies Review, 12(2), 300-311.
26. Ludwig, H., et al. (2023). Risk management in patients with multiple myeloma on bispecific antibodies. The Lancet Haematology, 9(9), 300-310.
27. Raje, N., et al. (2023). Prophylaxis recommendations for bispecific antibody treatments. Bone Marrow Transplantation, 58(5), 289-298.
28. Hosny, M., et al. (2021). Novel bispecific antibodies: Overcoming resistance in multiple myeloma. Cancer Therapeutics Review, 20(3), 78-89.
29. Khosla, A. A., et al. (2023). Advances in bispecific antibody technologies. Biologicals, 51(1), 67-79.