Review

Bispecific Antibodies for Multiple Myeloma: Recent Advancements and Strategies for Increasing Their Efficacy

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Abstract

The treatment options for multiple myeloma (MM) have undergone significant transformation with the advent of immunotherapy. Novel therapies that focus on tumor antigens now drive advances in MM research. Bispecific antibodies (bsAbs) leverage revolutionary advances in bioengineering techniques and embody the second generation of antibody-based tumor therapy. Recent studies on bsAbs in relapsed/refractory MM cases have revealed remarkable efficacy and acceptable safety profiles. The approval of elranatamab and teclistamab represents the next step in the development of bsAbs for the treatment of MM. This review article addresses the antigen targeting, efficacy, and strategies in the application of bsAbs against treatment-resistant MM, with a focus on clinical trials and real-world data.

Keywords: bispecific antibodies; multiple myeloma; immunotherapy; tumor antigens; resistance mechanism

1. Background

Multiple myeloma (MM) is the second most common hematologic malignancy in the United States, with an estimated 35,730 new cases and an estimated 12,590 deaths in 2023 [1]. The introduction of proteasome inhibitors, immunomodulatory drugs, and autologous stem cell transplant (ASCT) over the past decade has markedly improved the prognosis of MM, resulting in a median survival of 7 to 10 years [2–5]. Nevertheless, the majority of patients who initially respond eventually progress to a resistant state.

MM employs various strategies to reduce the host immune responses during disease progression, thereby enabling immune escape and uncontrolled cell proliferation. Consequently, immunotherapies, such as monoclonal antibodies (mAbs) and chimeric antigen receptor T-cell (CAR-T) therapies, have emerged as critical new pivotal approaches by reactivating the host immune system to eliminate tumor cells [6–8]. The dynamic landscape of antibody engineering has sparked interest in the development of bispecific antibodies (bsAbs). BsAbs concurrently target tumor-associated antigens (TAAs) and also engage effector cells through surface-associated molecules, thus triggering potent killing effects and sparking a surge in interest. In contrast to CAR-T therapy, bsAbs are readily scalable “off-the-shelf” products. In 2022, teclistamab received rapid approval from the U.S. Food and Drug Administration, becoming the first bsAb targeting CD3 and BCMA in MM, which has invigorated the field. This review article provides an in-depth examination of the advancements in bsAbs within the context of MM, with an emphasis on clinical studies and on potential strategies for enhancing their antitumor efficacy.

2. Structural Basis of BsAbs

BsAbs are broadly categorized into two main classes, characterized by the presence (IgG-like) or absence (non-IgG-like) of Fc domains [9,10]. IgG-like bsAbs are larger in size and therefore have a longer serum half-life [11]. Non-IgG-like bsAbs can readily penetrate tissues but must be continuously infused due to their shorter cycle kinetics [9,12]. Brinkman and Konterman [13,14] have comprehensively reviewed the ‘Zoo of BsAbs’, which comprises more than 100 distinct bsAb formats. Here we highlight the backbones of IgG-like and non-IgG-like bsAbs in Fig. 1 Ref. [9]. Apart from inhibiting multiple signaling pathways and mediating the formation of protein complexes, the major function of bsAbs is to recruit immunocompetent cells to the tumor environment and induce tumor lysis [15–19]. T cells play a crucial role in the anti-tumor action of immunotherapy [18]. In MM, the majority of bsAbs focus on T cell engineering through the CD3 receptor. There is also growing interest in the use of alternative constructs to engage with natural killer (NK) cells [20,21].

3. The Mechanism of Action of BsAbs

BsAbs generally have two binding sites, with one arm binding to the tumor-associated antigen (TAA) and the other arm simultaneously binding to CD3 molecules expressed on host T cells [22]. BsAbs mediate cell-cell adhesion...
Fig. 1. Different formats of bispecific antibodies. (A) IgG-like structure. IgG-like bispecific antibodies (bsAbs) mainly include Quadromas, DVD-Ig, IgG-scFv, Two in one IgG, Knobs-into-holes (Kih-assembly, Common light chain, Crossmab), Orthogonal Fab, \( \kappa \lambda \)-antibody. (B) Non-IgG-like structure. Non-IgG-like bsAbs mainly include bispecific T cell engager (BITE), Diabody, scFv2-albumin, TandAbs, DARTs, Nanobodies, Dock-and-lock (DNL) (Modified from reference [9]).

forces, thereby promoting the formation of more stable conjugates between target cells and effector cells, leading to a 3-fold increase in contact time to fully activate the T cell response [23]. The binding of bsAbs to target cells and effector cells can induce the formation of an immune synapse. This process is accompanied by the redistribution of signaling molecules and secretion granules within the cells, ultimately leading to the release of perforin, granzyme and cytokines including interleukin (IL)-2, IL-6 and interferon (IFN)-\( \gamma \) [24–26]. Perforin induces transient pore formation in target cells, and both perforin and granzyme are internalized into “nucleoli”. Perforin again forms pores in these enlarged endosomes, causing the release of granzymes into the cytoplasm to induce apoptosis in target cells [27]. This contact-dependent cytotoxicity serves as a major mechanism for directly killing of tumor cells.

4. Targeting Markers of MM Surface and the Relevant BsAbs

Achieving optimal effectiveness and high specificity hinges on the selection of the appropriate TAA when designing bsAbs. Ideally, the chosen TAA should meet these criteria: (a) Predominant expression on malignant cells, intricately linked to the malignant phenotype; (b) Essential role in tumor biology and/or pathophysiology; (c) Minimal presence in normal healthy cells [28]. This review highlights promising TAA candidates on the surface of MM cells (Fig. 2) that have attracted widespread attention.
Fig. 2. Targeting mechanisms of bispecific antibodies and promising markers in multiple myeloma. Bispecific antibodies simultaneously engage myeloma cells through specific tumor antigen (BCMA, GPRC5D, FcRH5, SLAMF7, CD38, CD138, CD19) and T cells or natural killer (NK) cells via CD3, CD16a or NKG2D and further promote direct cell-mediated cytotoxicity. IFNγ, interferon gamma; TNFα, tumor necrosis factor-alpha; IL-2, interleukin 2; MM, multiple myeloma.

4.1 BCMA

BCMA is a transmembrane glycoprotein belonging to the tumor necrosis factor receptor superfamily 17. It is selectively expressed on the surfaces of plasma blasts and differentiated plasma cells. BCMA interacts with two agonist ligands, a proliferation-inducing ligand and B cell activating factor. This interaction activates p38/NF-κB pathways, leading to the upregulation of anti-apoptotic proteins that modulate B cell maturation, proliferation, and survival [29–33]. Furthermore, overexpression of BCMA can trigger the activation of NF-κB and MAPK pathways in MM cells, even without stimulation with the two ligands [32]. BCMA shows consistent expression in MM cell lines and primary patient samples, with varying intensities among different patients. Elevated serum concentrations of BCMA correlate closely with an immunosuppressive phenotype and worse clinical outcomes [33]. BCMA stands out as the most promising TAA in MM, and several bsAbs therapies showing favorable efficacy in clinical trials are described below.

4.1.1 Elranatamab

Elranatamab is a humanized IgG bsAb that binds to BCMA+ myeloma cells and CD3+ T cells [34]. The MagnetisMM-1 trial (NCT03269136) involved 55 patients who received monotherapy with effective doses of elranatamab. The overall response rate (ORR) was 63.6%, with 38.2% of patients achieving complete response (CR) or better. Among patients who were previously treated with BCMA-targeted therapies, 53.8% showed a response to elranatamab. No dose-limiting toxicities were observed during dose escalation. Adverse events (AEs) included cytopenia and cytokine release syndrome (CRS), with exposure proportional to the dose [35]. The MagnetisMM-3 trial (NCT04649359) showed an ORR of 61.0% in 123 patients who received subcutaneous (SC) elranatamab, with 35.0% achieving CR or better. Of 50 responders who switched to biweekly dosing, 40 maintained/improved their response for ≥6 months. The median duration of response (mDOR), progression-free survival (PFS), and overall response (OS) are unreached with a median follow-up of 14.7 months. Frequent AEs included infections (69.9%), CRS (57.7%), anemia (48.8%), and neutropenia (48.8%) [36,37]. The health records of patients from the MagnetisMM-3 trial were compared with data from 391 MM patients in real-world clinical practice contained in two American databases. Compared to standard care, MM patients treated with elranatamab showed better ORR and longer PFS [38]. Another study compared patient data from the MagnetisMM-3 trial with published summary data from two real-world studies (LocoMMotion and MAMMOTH) on physician’s choice of treatment (PCT) in patients with relapsed or refractory MM (RRMM). In the comparative analysis, elranatamab consistently showed improved response rates and depth, as well as significantly longer PFS and OS compared to PCT [39]. Elranatamab is currently approved for clinical use in RRMM patients in the United States, the European Union, and Canada.
4.1.2 Teclistamab

Teclistamab is a humanized IgG bsAb that targets BCMA and CD3 [40]. The MajesTEC-1 trial (NCT04557098) found that teclistamab exhibits promising clinical activity, with an ORR of 63% and a CR or better achieved in 39.4% of patients. The most common AEs were CRS (72%), neutropenia (71%), and anemia (55%) [41,42]. Teclistamab has been approved for patients with RRMM who have received ≥4 prior therapies, including immunomodulatory drugs (IMIDs), proteasome inhibitors, and CD38 antibodies. Many real-world studies have reported effective outcomes with teclistamab. An analysis of teclistamab therapy at 7 international myeloma academic centers showed an ORR of 63%, with a CRS incidence similar to that reported in the MajesTEC-1 study [43]. A multicenter retrospective study of 45 patients with RRMM revealed significant clinical activity with teclistamab [44]. Analysis of 123 German patients with RRMM showed that teclistamab achieved an ORR of 59.3% in all patients, and 64.5% in those who had not received prior anti-BCMA treatment [45]. A retrospective analysis of 89 RRMM patients treated with teclistamab at five academic centers in the United States revealed an ORR of 55%, with ≥37% of cases achieving very good partial response (VGPR) [46]. Another study conducted at five academic centers in the United States investigated the toxicity and efficacy of teclistamab in RRMM patients aged ≥70 years. The results showed that age ≥70 years did not impact response outcomes or PFS. Although patients aged ≥70 years are more likely to experience grade 3–4 thrombocytopenia, no significant difference was found in the infection rate compared to younger patients [47]. These data support the use of teclistamab in elderly RRMM patients. Moreover, a retrospective study suggested that teclistamab is a viable, effective, and safe choice for RRMM patients requiring dialysis [48].

4.1.3 Alnuctamab (ALNUC; CC-93269)

Alnuctamab is an asymmetric, two-arm, humanized IgG trivalent bsAb that binds bivalently to BCMA and monovalently to CD3 [49–51]. A Phase 1 trial (NCT03486067) found that RRMM patients who received intravenous (IV) alnuctamab had a median response duration of 33.6 months. However, due to the occurrence of CRS in 76% of patients, the study shifted to SC treatment. As of April 3, 2023, 73 patients undergoing SC alnuctamab treatment exhibited an ORR of 54% across all doses, with deepening responses over time. The ORR reached 63% at the target dose of ≥30 mg, with all 14 assessable samples being Minimal residual disease (MRD) negative. Forty percent of patients experienced CRS after the first incremental dose, with the rate decreasing to less than 1% per dose from the fourth dose onwards. These results indicate that SC alnuctamab significantly enhances safety while demonstrating promising anti-tumor activity [52,53].

4.1.4 ABBV-383 (TNB-383B)

ABBV-383 is a fully human IgG4 bsAb generated using knob-in-hole technology. ABBV-383 exhibited promising activity in a Phase 1 study (NCT03933735) [54]. An updated study reported the results of the dose expansion study for IV ABBV-383. ABBV-383 demonstrated deep and enduring responses at doses of 40 mg and 60 mg, with a median PFS of 13.7 months and 11.2 months, respectively, and 12-month duration of response (DOR) rates of 70% and 66%, respectively. At doses of 20 mg, 40 mg, and 60 mg, the incidence rates of CRS and of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) were 50%/3%, 71%/5%, and 70%/5%, respectively. Further clinical evaluation of ABBV-383 is ongoing [55].

4.1.5 Livoseltamab (REGN5458)

Livoseltamab is a bsAb displays comparable antitumor efficacy to anti-BCMA CAR-T cells [56]. Preliminary results from the LINKER-MM1 (NCT03761108) study indicated that treatment with livoseltamab elicited deep and enduring responses in patients, with a low incidence of CRS [57]. The updated data reported the efficacy in the cohort using 200 mg livoseltamab, with ORR and CR rates of 70% and 29% for patients with ≥ grade 3 refractory diseases, respectively. The most common treatment-related AEs (TRAEs) are CRS, followed by cough (33%), neutropenia (32%), diarrhea (32%), and fatigue (32%), etc. The Phase 2 study of livoseltamab in the treatment of high-risk smoldering MM (LINKER-SMM1, NCT05955508) is ongoing [58].

4.1.6 RO7297089

RO7297089 is a bsAb targeting BCMA and CD16a [59]. The Phase 1 study’s (NCT04434469) findings showed that administering RO7297089 through IV at weekly doses ranging from 60 to 1850 mg in RRMM patients maintained an acceptable safety profile. However, the observed single-agent efficacy of RO7297089 is less robust than that reported with BCMA bsAbs [60]. This possibly results from RO7297089’s extended half-life, which might gradually dampen NK cell function over time, causing a state of hyporesponsiveness and limiting response to repeated infusions [61]. Optimizing dosage or exploring combination strategies might be necessary to advance its clinical development. Combining RO7297089 with agents that enhance NK cell activity presents an intriguing avenue to potentially enhance responses achieved with RO7297089 alone [62].

4.1.7 WVT078

WVT078 is a potent anti-BCMA×anti-CD3 bsAb. Monotherapy with WVT078 has demonstrated acceptable safety in an ongoing study (NCT04123418), with an ORR of 38.5% at doses ranging from 48 to 250 μg/kg and 75% at the highest tested dose. BCMA is cleaved by Gamma-Secretase to produce soluble BCMA (sBCMA), which can
bind to BCMA-targeting drugs and interfere with their activity. Therefore, Gamma-Secretase inhibitor (GSI) is considered to potentially enhance the clinical benefits of BCMA-targeting drugs. Schjesvold et al. [63] reported the effects of WVT078 in combination with the GSI WHG626 in RRMM. According to preliminary data, compared to using WVT078 alone, the WVT078 + WHG626 combination observed cytokine and clinical effects at lower doses of WVT078, supporting the combination therapy of BCMA-targeting bsAbs with GSIs in the treatment of RRMM [64].

4.1.8 F182112

F182112 is an anti-BCMA×anti-CD3 bsAb. In the NTP-F182112-001 (NCT04984434) trial, 22 patients received treatment with F182112 at eight escalating dose levels ranging from 0.01 to 30 µg/kg. The ORR was 45%, with an ORR of 77.8% observed in the 10 µg/kg and 20 µg/kg dose groups. 82% of patients reported TRAEs, with 64% experiencing grade 3 or higher AEs. The most common AEs at doses of 0.4 mg/kg weekly or 0.8 mg/kg every two weeks demonstrated ORRs of 86.7% and 83.3%, respectively. The most common AEs were dysgeusia (77.1%), CRS (74.3%; mostly grade 1/2, 2.9% grade ≥3) and neutropenia (60.0%). Talquetamab in combination with daratumumab also showed synergistic efficacy [75]. In TRIMM-2 (NCT04108195), 65 patients received talquetamab at 0.4 mg/kg or 0.8 mg/kg every 2 weeks, accompanied by SC daratumumab. The ORR was 78%, and the most AEs included CRS (78%; all G1/G2), dysgeusia (75%), dry mouth (55%), anemia (52%), skin exfoliation (45%), and fatigue (45%) [76].

Another promising anti-GPRC5D×anti-CD3 bsAb currently under development is forimatim (RG6234/RO7425781). In a Phase 1a dose-escalation trial (BP42233, NCT04557150) in RRMM patients, forimatim induced deep and durable responses, with a mDOR of 12.2 months. Forimatim achieved an ORR of 66.7% across all dose levels, with a VGPR rate of 54.2%. No new safety signals related to CRS, rash, or other on-target events were observed [77]. Two new anti-GPRC5D×anti-CD3 bsAbs (LBL-034 and BR109) have also been developed and undergone preclinical studies, with a clinical trial for LBL-034 already scheduled [78,79].

4.2 GPRC5D

GPRC5D is characterized as a C7-type transmembrane receptor and shows highly specific expression in plasma cells [66,67]. Its close proximity to the plasma membrane enhances the immune synapse between T cells and target cells, fostering more potent cytotoxicity. Given its 7-pass transmembrane nature, GPRC5D is unlikely to shed into the serum. This contrasts with other surface antigens such as BCMA, where shedding can lead to sedimentation effects and reduced efficacy [68]. The mRNA expression of GPRC5D correlates with plasma cell burden and genetic variations, such as chromosome 13q14 deletion and translocation t(4;14) [66]. The exclusive presence of GPRC5D on MM cells suggests it may be a potential target for bsAb therapy [69,70].

Talquetamab (JNJ-64407564) is a first-in-class bsAb that combines CD3 and GPRC5D. The activity of talquetamab in H929 cells is not affected by BCMA loss, suggesting that patients who are resistant to BCMA therapy or have low/absent BCMA expression may be treated with talquetamab [71]. The Phase 1/2 MonumenTAL-1 study (NCT03399799/NCT04634552) reported an ORR of over 71% in 288 patients who had not received prior T cell redirecting therapy (TCR) treatment. Among 143 patients treated with 0.4 mg/kg weekly, the ORR was 73%. The most common AEs at doses of 0.4 mg/kg or 0.8 mg/kg were CRS (79%/72%), dysgeusia (48%/46%), and anemia (45%/39%) [72]. Of the 135 patients who discontinued talquetamab in MonumenTAL-1, various treatment modalities including TCR were also found to be effective, with 25.0% of patients achieving CR or better after CAR-T therapy [73]. In 70 patients who were previously treated with TCR therapies including anti-BCMA-CAR-T, anti-BCMA bsAb, or BCMA-ADC, talquetamab demonstrated robust efficacy, with an ORR of up to 73%. More than 50% of patients previously exposed to bsAbs showed a response. These results indicate that talquetamab provides durable responses for TCR/BCMA-naïve and TCR/BCMA-exposed patients with RRMM [74]. In addition to monotherapy, researchers also investigated the efficacy of talquetamab combined with IMiDs and the anti-CD38 monoclonal antibody daratumumab. Talquetamab in combination with pomalidomide (MonumenTAL-2, NCT05050097) at doses of 0.4 mg/kg weekly or 0.8 mg/kg every two weeks demonstrated ORRs of 86.7% and 83.3%, respectively. The most common AEs were dysgeusia (77.1%), CRS (74.3%; mostly grade 1/2, 2.9% grade ≥3) and neutropenia (60.0%). Talquetamab in combination with daratumumab also showed synergistic efficacy [75]. In TRIMM-2 (NCT04108195), 65 patients received talquetamab at 0.4 mg/kg or 0.8 mg/kg every 2 weeks, accompanied by SC daratumumab. The ORR was 78%, and the most AEs included CRS (78%; all G1/G2), dysgeusia (75%), dry mouth (55%), anemia (52%), skin exfoliation (45%), and fatigue (45%) [76].

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4.3 FcRH5

Fc receptor-homolog 5 (FcRH5) is a type I membrane protein belonging to an immunoglobulin superfamily with six genes [80–82]. FcRH5 is expressed exclusively on the surface of B cells and plasma cells, with an almost 100% prevalence on MM cells [26]. FcRH5 is expressed consistently throughout MM progression [83]. Gain of chromosome 1q21 is one of the most frequent genetic anomalies in MM and is prognostic for invasive disease [84]. FcRH5 was initially identified in clones from this chromosomal region and was found to be deregulated in cell lines exhibiting 1q21 abnormalities [85]. Primary samples from MM patients with 1q21 gain show elevated FcRH5 gene expression, suggesting that targeting FcRH5 may yield clinical benefit for this subgroup [26].

With regard to bsAbs targeting FcRH5, the large size of the FcRH5 extracellular region could lead to an increased distance between the antigen epitope and the tar-
get membrane, thus potentially hindering the effective formation of T cell synapses [86]. Li et al. [26] developed a humanized IgG-based bsAb, cevostamab, that targets the most membrane-proximal domain of FcRH5 on MM cells and CD3. In a Phase 1 trial (GO39775, NCT03275103), cevostamab showed meaningful activity and a favorable safety profile when administered Q3W for up to 17 cycles. Patients achieved durable responses (≥6 months) beyond the 17-cycle treatment. Among 16 patients analyzed, the best OS included stringent CR in 7 patients, CR in 3 patients, VGPR in 5 patients, and PR in 1 patient. These findings suggest the potential for an extended treatment-free period after fixed-duration cevostamab therapy [87]. A Phase 2 study (NCT05801939) is exploring the efficacy of consolidation therapy with cevostamab following BCMA CAR-T treatment, with the aim of eliminating residual disease by targeting two different antigens [88].

4.4 CD38

CD38 is a transmembrane glycoprotein characterized by high surface density and consistent expression on MM cells. CD38 expression is relatively low in normal myeloid and lymphocytes [89,90]. The clinical success of monoclonal antibodies targeting CD38 has stimulated the corresponding development of bsAbs. [91]. VP301 is a novel bsAb that targets CD38 and intercellular adhesion molecule 1. In vitro and in vivo experiments have shown promising activity of VP301 against primary MM samples. VP301 also exhibits synergistic anti-tumor growth activity when used in combination with the immunomodulatory drug lenalidomide [92]. ISB 1342 is a bsAb that targets CD3 and CD38. In preclinical studies, ISB 1342 demonstrated greater tumor eradication compared to daratumumab [93,94]. A Phase 1 study (NCT03309111) evaluated 39 subjects receiving IV ISB 1342 and 7 subjects receiving SC ISB 1342. T cell activation was observed following administration of ISB 1342 at doses of 1.0/4.0 mg/kg and higher for 24–48 hours. Moreover, 89% of subjects experienced TRAEs, mostly grades 1–2, including infusion-related reactions (37%), CRS (34%), anemia (24%), neutropenia (24%), and thrombocytopenia (17%) [95]. ISB 1442 is a fully humanized bsAb that targets CD38 and CD47. Preliminary results of a Phase 1/2 study (NCT05427812) in RRMM patients reported on 10 subjects who received weekly SC ISB 1442. ISB 1442 demonstrated good tolerability at the evaluated dose levels. The observed clinical CRS events were moderate and were potentially associated with macrophage activation following ISB 1442 administration [96].

4.5 SLAMF7

SLAMF7, or CS1/CD319, is a cell surface glycoprotein expressed exclusively on plasma cells, NK cells and a subset of activated T cells [97,98]. SLAMF7 is a vital regulator of normal immune cell function and activates NK cells, promotes the growth of normal B cells, and inhibits T cell development [99]. Notably, SLAMF7 can drive tumor progression by facilitating the adhesion of MM cells to bone marrow stromal cells (BMSCs) within the microenvironment, thus making it a promising target for MM therapy [98,100]. Chan engineered a non-IgG-like, scFv-based bsAb that targets SLAMF7 and NKG2D and can activate all NKG2-expressing immune cells, including NK cells, CD8\textsuperscript{+} T cells, γδT cells and NKT cells. This bsAb induced specific killing of SLAMF7\textsuperscript{+} MM cells and significantly prolonged survival time in NSG mouse models [20]. Lum et al. [101] used a bsAb against SLAMF7 and CD3 to activate T cells from normal donors or MM patients. When co-cultured with MM cell lines, this bsAb showed potent killing efficacy accompanied by the release of Th1 cytokines, chemokines, and granzyme B [101]. A Phase 1/2 study of this bsAb armed fresh peripheral blood mononuclear cells in RRMM is ongoing (NCT04864522).

4.6 CD138

CD138 is a single-pass, type I membrane protein from the syndecan proteoglycan family. It is widely expressed in epithelial cells and plays a role in the proliferation, adhesion, and migration of diverse types of malignant tumors [102]. The notable expression of CD138 on MM cells and its favorable influence on the disease phenotype make it a compelling target for targeted therapy [103,104]. von Strandmann et al. [21] developed the bsAb ULBP2-BB4, which fuses an anti-CD138 scFv with ULBP2, a ligand for NKG2D receptors on NK cells. ULBP2-BB4 enhanced the NK-mediated cleavage of MM cells and suppressed tumor growth in nude mouse models [21]. STL001 features nanomolar affinity for recombinant CD138 protein and exhibits robust anti-MM activity, both in vitro and in vivo [105]. However, the widespread expression of CD138 on epithelial cells in addition to MM cells presents a challenge. Phase 1 clinical trials of anti-CD138 antibody conjugates have reported related AEs, including hand-foot syndrome, stomatitis, and blurred vision [106]. Additionally, the shedding of sCD138 and its accumulation in the BM may reduce the efficacy of bsAbs that target tumor cells by neutralizing their effects. At present, there are no ongoing clinical trials involving CD138 bsAbs.

4.7 CD19

CD19 is expressed on B cells during their development, but diminishes during plasma cell differentiation [107,108]. The majority of malignant plasma cells lack CD19 expression, with only around 10% belonging to the CD19\textsuperscript{+} subgroup [109]. Consequently, CD19 is not generally regarded as a prime immunotherapeutic target for MM. Nonetheless, some reports indicate that a minor fraction of MM clones with drug resistance and disease-propagating traits maintain a B cell (CD19\textsuperscript{+}) phenotype [110], and myeloma cells more frequently exhibit low levels of CD19...
expression. In vitro studies have demonstrated cytotoxicity of CD19-targeting CAR-T cells against MM cells with very low levels of CD19 expression [111]. Furthermore, sustained remission was obtained in one patient with advanced MM who received anti-CD19 CAR-T cells in combination with ASCT [112]. In addition, combined application of anti-BCMA and anti-CD19 CAR-T therapy in RRMM patients resulted in a strong therapeutic effect and was associated with negative MRD [113]. These findings suggest that bsAbs targeting CD19 may be an option for MM. Although the Phase 1 clinical trial of blinatumomab (NCT03173430) in patients with advanced MM after ASCT was terminated prematurely due to slow accrual, the use of CD19 bsAbs in myeloma therapy warrants further clinical evaluation.

5. Summary of Clinical Efficacy and Safety Profiles

Overall, bsAbs show promising efficacy results with generally manageable AEs. Moreover, the ORR for a monotherapy used in such heavily pretreated patients is impressive, with most trials having a median of 6 prior lines. Studies on teclistamab and talquetamab showed favorable ORR of 63% [42] and 73% [114], respectively. The DOR is evolving in most studies, as many subjects are still alive and responding. In evaluable patients, MRD negativity has ranged from 46% to 100% [42,52]. With increased clinical testing, the safety data for bsAbs are becoming more comprehensive. While the overall safety of bsAbs is manageable, some side effects require significant attention. Infection and hematologic-related AEs are relatively common, with the latter sometimes causing infections that represent a significant clinical burden. The efficacy and safety of monotherapy trials for some promising bsAbs are summarized in Table 1. MM patients typically experience secondary immune deficiencies such as hypogammaglobulinemia (HGG), with low serum IgG levels and an increased risk of bacterial infections [115]. Studies have found that treatment with bsAbs can prolong the course of HGG and thus increase the risk of infection [116]. Targeting BCMA often leads to profound B-cell depletion. For example, in patients receiving BCMA-targeted therapy, antibody responses to COVID-19 vaccines are particularly weak [117]. Therefore, serious infections in patients who receive bsAbs targeting BCMA should be considered as potentially treatment-related. In MajesTEC-1, 19 patients (11%) died from infections, with 5 of these attributed to teclistamab [42]. The incidence of treatment-related infections in the ABBV-383 trial was 41%, with 20% being grade 3 infections (pneumonia, COVID-19, sepsis, urinary tract infection). However, 7 deaths from COVID-19 and one death from sepsis were considered to be unrelated to ABBV-383 [118].

Current recommendations regarding monotherapy and combination therapy with bsAbs are based primarily on data from studies of teclistamab and elranatamab. BsAbs that target different antigens may have varying infection rates and risks, depending on the dosage, dosing interval, and patient characteristics [119]. Compared to GPRC5D-bsAb monotherapy, BCMA-bsAb monotherapy or GPRC5D-bsAb combination therapy were found to have a higher cumulative incidence of infections, and were associated with more grade 3 infections [120]. In the small phase I/II TRIMM-2 study, the incidence of infections with teclistamab or talquetamab in combination with daratumumab was similar to that of monotherapy [121,122]. However, in the MajesTEC-2 trial in which teclistamab was combined with daratumumab and lenalidomide, 90.6% of patients experienced any grade infection, and 37.5% experienced grade 3/4 infections [123]. Expert consensus has suggested similarities in infection monitoring and prevention between bsAb and CAR-T cell therapy [124]. However, it should be noted that bsAbs carry their own individual infection risk [119]. The mechanism of cytopenia is unclear, with one hypothesis postulating a bystander effect of cytokine release and marrow plasma cell destruction [125]. CRS is a key toxicity reported for all bsAbs, with an overall incidence as high as 87% [126]. Almost all grade 3 CRS cases were confined to 3% [42,114,127]. Moreover, CRS associated with almucntamab treatment can result in fatal outcomes [51]. CRS manifests primarily after the initial injection and is self-limiting [57]. It necessitates only supportive care with antipyretics and IV fluids. In some intensive cases, CRS can be controlled by dexamethasone and tocilizumab [42,52,128]. The major risk factors for CRS are tumor load and the initial dose of bsAbs [129]. Hypoxia and abnormal liver function were also found to be drivers of grade 3 CRS [130], and the use of an incremental dosing regimen can reduce the risk of severe CRS [131]. Following the use of teclistamab, patients with a history of TCR therapy had a significantly lower incidence of CRS than those with no prior TCR therapy, possibly due to T-cell exhaustion [132]. With elranatamab, the presence of extramedullary disease and prophylactic use of tocilizumab were associated with a reduced incidence of CRS [133]. ICANS is also a common side effect, and has been documented with the use of elranatamab [36], teclistamab [42], linvoseltamab [57], talquetamab [134] and cevostamab [127]. Some cases with ICANS were observed concurrently with CRS, but subsided once the CRS had resolved. In RRMM patients receiving teclistamab, the prophylactic use of tocilizumab before dose escalation reduced the incidence and severity of CRS and decreased the occurrence of ICANS [135,136]. Serious AEs such as fatigue [36,42,57], pyrexia [42], back pain [42,59], diarrhea [36] and hypokalemia [36] were also reported. Additionally, because some cells in the oral mucosa express GPRC5D, patients treated with talquetamab may experience taste changes, thereby affecting their quality of life and nutritional status [137]. Researchers found that patients who received GPRC5D bsAbs experienced significant taste impairment, leading to reduced appetite, weight
Table 1. A summary of the efficacy and safety of monotherapy trials of some promising bsAbs.

<table>
<thead>
<tr>
<th>Agents</th>
<th>Patient Characteristics</th>
<th>Response Rates</th>
<th>TRAEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elranatumab MagnetisMM-1</td>
<td>(1) RRMM (n = 55), SC monotherapy at dose levels ≥215 µg/kg with 11 ongoing;</td>
<td>(1) ORR: 63.6%, VGPR or better: 56.4%, CR or better: 38.2%;</td>
<td>(1) Hematologic: Neutropenia (74.5%), Anemia (67.3%), Lymphopenia (52.7%), Thrombocytopenia (50.9%);</td>
</tr>
<tr>
<td>NCT03269136</td>
<td>(2) Median age: 64.0 years old;</td>
<td>mPFS: 11.8 months, mOS: 21.2 months, mDOR: 17.1 months,</td>
<td>(2) Non-hematologic: CRS (87.3%, G1–G2), Injection site reaction (56.4%), Fatigue (41.8%), Diarrhea (40%), Dry skin (36.4%), Hypophosphatemia (36.4%), Decreased appetite (34.5%), Nausea (34.5%)</td>
</tr>
<tr>
<td>BCMA×CD3</td>
<td>(3) Median lines of prior regimens: five;</td>
<td>(3) 13 patients with confirmed CR or better, all MRD negative</td>
<td></td>
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<tr>
<td></td>
<td>(4) 90.9% were triple-class refractory, 29.1% had high cytogenic risk, 23.6% had received prior BCMA-directed therapy</td>
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<tr>
<td>Elranatumab MagnetisMM-3</td>
<td>(1) RRMM (n = 123), SC elranatumab;</td>
<td>(1) ORR: 61%, VGPR or better: 56.1%, CR or better: 35%;</td>
<td></td>
</tr>
<tr>
<td>NCT04649359</td>
<td>(2) Median age: 64.0 years old;</td>
<td>mPFS and mDOR were not reached, estimate of mPFS and mDOR at 15 months was 50.9% and 56.7%,</td>
<td></td>
</tr>
<tr>
<td>BCMA×CD3</td>
<td>(3) Median lines of prior regimens: five;</td>
<td>(2) Non-hematologic: CRS (57.7%, no G3–G4), Diarrhea (42.3%), Fatigue (36.6%), Decreased appetite (33.3%), Pyrexia (30.1%), Covid-19 (29.3%), Injection site reaction (26.8%), Nausea (26.8%), Hypokalemia (26%), Cough (25.2%), Headache (23.6%)</td>
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<tr>
<td></td>
<td>(4) No prior BCMA-directed therapy, 96.7% were triple-class refractory, 25.2% had high cytogenic risk</td>
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<tr>
<td>Teclistamab MajesTEC-1</td>
<td>(1) RRMM (n = 165), QW SC teclistamab at a dose of 1.5 mg/kg;</td>
<td>(1) ORR: 63%, VGPR or better: 58.8%, CR or better: 39.4%;</td>
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<tr>
<td>NCT03145181</td>
<td>(2) Median age: 64 years old;</td>
<td>mPFS: 11.3 months, mOS: 18.3 months, mDOR: 18.4 months,</td>
<td></td>
</tr>
<tr>
<td>NCT04557098</td>
<td>(3) Median lines of prior regimens: five;</td>
<td>(3) MRD negativity was 89.7% in 29 patients with confirmed CR</td>
<td></td>
</tr>
<tr>
<td>BCMA×CD3</td>
<td>(4) 77.6% were triple-class refractory, 25.7% had high cytogenic risk</td>
<td>(1) Hematologic: Neutropenia (70.9%), Anemia (52.1%), Lymphopenia (34.5%), Leukopenia (17.6%);</td>
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<td>(2) Non-hematologic: CRS (72.1%, 0.6% in G3–G4), Neurotoxic event (14.5%), Fatigue (27.9%), Diarrhea (28.5%), Nausea (27.3%), Injection site erythema (26.1%), Pyrexia (27.3%), Headache (23.6%), Arthralgia (21.8%), Constipation (20.6%) Cough (20%), Pneumonia (18.2%), Covid-19 (17.6%), Bone pain (17.6%), Back pain (16.4%)</td>
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<tr>
<td>Agents</td>
<td>Patient Characteristics</td>
<td>Response Rates</td>
<td>TRAEs</td>
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<tr>
<td>Talquetamab</td>
<td>(1) RRMM (n = 30, at 405 µg QW) or (n = 44, at 800 µg Q2W); (2) Median age, 64.0 years old; (3) Median lines of prior regimens: six; (4) 99% were triple-class refractory, 16% had high cytogenetic risk</td>
<td>dosage of 405/800</td>
<td>dosage of 405/800</td>
</tr>
<tr>
<td>MonumenTAL-1 NCT03399799 GPRC5D×CD3</td>
<td></td>
<td>(1) ORR: 70%/64%, VGPR or better: 57%/52%; (2) mPFS: 7.5/11.9 months, mOS: 76.4%/77.4% at 12 months, mDOR: 9.5 months/NR</td>
<td>(1) Hematologic: Anemia (60%/43%), Neutropenia (67%/36%), Lymphopenia (40%/39%), Thrombocytopenia (37%/23%), Leukopenia (40%/18%); (2) Non-hematologic: CRS (77%/80%, only one patient in G3–G4 at 405 dosage), Skin-related event (67%/70%), Dysgeusia (63%/57%), Fatigue (33%/27%), Nail-related event (57%/27%), Pyrexia (33%/18%), Headache (20%/25%), Rash-related event (47%/30%), Diarrhea (30%/16%), Cough (20%/11%), Dry mouth (30%/57%), Nausea (30%/16%), Arthralgia (23%/9%), Decreased weight (30%/32%), Increased alanine aminotransferase (20%/30%), Increased aspartate aminotransferase (10%/34%), Back pain (10%/20%), Hypophosphatemia (27%/18%), Dysphagia (37%/27%), Decreased appetite (20%/20%), Constipation (7%/14%), Increased γ-glutamyltransferase (20%/23%)</td>
</tr>
<tr>
<td>Cevostamab</td>
<td>(1) RRMM (n = 160); (2) Median age, 64.0 years old; (3) Median lines of prior regimens: six; (4) 85% were triple-class refractory</td>
<td>(1) ORR: 54.5%/36.7% (160 mg/90 mg); (2) mDOR: 15.6 months,</td>
<td>(1) Hematologic: Neutropenia (18.1%), Anemia (31.9%); (2) Non-hematologic: CRS (80%, 1.3% in G3–G4), Infections (42.5%), Neurological/Psychiatric (40.6%), Diarrhea (26.3%), Cough (23.1%), Nausea (21.9%), Infusion-related reaction (17.5%), Fatigue (16.3%), Increased aspartate aminotransferase (15.6%), Hypomagnesaemia (15.6%), Pyrexia (15.6%), Increased alanine aminotransferase (15%)</td>
</tr>
<tr>
<td>NCT03275103</td>
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<td>FcRHS×CD3</td>
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</table>

**Table 1. Continued.**

TRAEs, treatment-related adverse events; RRMM, relapsed or refractory multiple myeloma; SC, subcutaneous; ORR, overall response rate; VGPR, very good partial response; CR, complete remission; mPFS, median progression-free survival; mOS, median overall survival; mDOR, median duration of response; MRD, minimal residual disease; NR, not reached; QW, weekly; Q2W, every 2 weeks; CRS, cytokine releasing syndrome.
loss, and dry mouth [138]. Despite these toxicities, the health-related quality of life of RRMM patients treated with bsAbs was found to improve [139]. As bsAbs become more widely used in the clinic, their efficacy and safety profiles will be better defined in the coming years.

6. Evasion Strategies and Improving the Efficacy of BsAbs

Cancer is a heterogeneous disease that employs diverse evasion strategies over time to adapt to its environment. The potent selective pressure exerted by bsAbs can drive myeloma blasts to adopt specific and extreme escape strategies. Plausible mechanisms for this include antigen loss, an immunosuppressive tumor microenvironment (TME), and the absence of costimulatory domains [22]. The short cycle kinetics of bsAbs could be perceived as a limitation. Researchers are exploring genetic approaches for the in-situ generation of bsAbs that circumvent the need for continuous drug infusion and partly counter the immunosuppressive TME. This section explores the resistance mechanisms to bsAbs, as well as strategies that could enhance their efficacy.

6.1 Antigen Loss

Tumor antigens play a pivotal role as distinctive markers that serve as the primary target for various immunotherapies. The selection of a suitable target antigen is a pivotal step in ensuring the efficacy and precision of immunotherapy. However, to evade immune attack by bsAbs, tumor cells often manipulate their surface properties by reducing antigen expression, or even translocating the tumor antigen to the effector T cell surface [140]. At the gene level, monoallelic deletions, biallelic deletions, or mutations can reduce expression of the target antigen. In addition, quantitative and structural changes at the chromosomal level can reduce TAA expression, or even cause total loss of expression. So far, three cases of BCMA genomic loss have been reported, all of which exhibited a similar mechanism of biallelic loss as the TNFRSF17 gene. This included extensive prior loss of chromosome 16p, followed by a second focal genomic hit on the remaining allele [141–143]. Monoallelic GPRC5D frameshift and missense mutations can occur in up to 15% of MM patients, and patients with monoallelic GPRC5D deletion may have a specific risk of developing resistance to teclistamab [141,144]. In the study by Lee et al. [145], 6 of 14 patients (42.8%) experienced disease progression following anti-BCMA bsAb treatment, with several TNFRSF17 mutation events observed. Moreover, GPRC5D biallelic mutations leading to GPRC5D loss were found among the 4 patients who relapsed after anti-GPRC5D bsAb treatment [145].

Another potential mechanism associated with BCMA loss is interference by sBCMA. A recent study by Chen et al. [146] suggested that high serum levels of sBCMA may decrease the ability of anti-BCMA antibodies to bind to tumor cells in patients with RRMM. Most RRMM patients have elevated sBCMA, which can significantly reduce BCMA on the surface of MM cells and thus down-regulate the functionality of BCMA in these patients. Inhibition of γ-secretase activity can upregulate BCMA density on plasma cells, thereby enhancing the efficacy of in vivo anti-BCMA CAR-T cell therapy [147]. The targeting of γ-secretase may therefore be a strategy to increase the activity of anti-BCMA bsAbs. Focusing solely on a single TAA could render the chosen target susceptible to genetic alterations, thereby undermining the effectiveness of immunotherapy and ultimately resulting in the emergence of drug resistance [22]. To counteract the potential immune anergy associated with single-antigen targeting, the co-targeting of multiple markers is attracting attention. This strategy allows the simultaneous recognition of various antigens on the surface of cancer cells, thereby enhancing both affinity and specificity [148]. Researchers have found that co-expression of GPRC5D, FcRH5, and BCMA is widespread in bone marrow samples from MM patients undergoing forintamig treatment. This suggests that targeting multiple MM surface markers may result in dual/triple targeting of individual tumor cells [149]. Another approach involves the identification of neoantigens through genomics, proteomics, or cell-based functional methods, with the aim of achieving enhanced specificity and efficacy [150].

6.2 Immunosuppressive Microenvironment

The intricate interaction between myeloma cells and the BM microenvironment is pivotal for sustaining the growth of myeloma cells and suppressing apoptosis [151,152]. The accumulation of malignant myeloma cells contributes to a high tumor burden and promotes tumor progression and drug resistance. Longitudinal analysis of the bone marrow T-cell repertoire and its response to bsAb therapy-induced perturbations revealed that the state of T cells and tumor recognition are prerequisites for the expansion of clone T cells and clinical responses. Most CD4+ T cells do not exhibit clonal expansion in response to bsAbs. Over-expanded CD8+ or CD4+ T cell clones are not exhausted in responsive patients, whereas T cell clones in non-responders are in a state of exhaustion [153]. Currently, both bsAbs and CAR-T therapies are considered 4th-line treatments in MM. Exposure to either may lead to T-cell exhaustion, thereby affecting the efficacy of the other. Researchers should therefore consider the sequence in which bsAbs and CAR-T therapies are given, with some clinical data supporting sequential treatment of these two therapies. After treatment with bsAbs and disease relapse, MM patients given sequential CAR-T therapy show an ORR of >80% and a more durable response compared to traditional therapies [154]. Elranatamab is effective in RRMM patients after BCMA CAR-T, thus supporting BCMA-targeted retreatment of patients with good
T cell status [155]. Patients who are responsive to teclistamab exhibit distinct immune characteristics, with higher levels of transient T cell activation. In contrast, non-responders consistently display a phenotype of T cell exhaustion, with higher frequencies of γδ T cells and immunosuppressive Tregs [156]. The efficacy of teclistamab was found to be slightly lower in patients previously treated with anti-BCMA therapies, with Tregs associated with non-responsiveness. Blocking TIGIT or depleting CD25+ cells may enhance the potential therapeutic effects of bsAbs [157]. In MonumenTAL-1, patients who had not received prior TCR therapy exhibited less T cell dysfunction and less immune suppression compared to patients previously treated with TCR. Mechanisms of resistance to talquetamab in non-responders included lower T cell counts, higher frequencies of Tregs, and the expression of co-inhibitory markers on CD8+ T cells. Patients who experienced relapse showed an exhausted T cell phenotype. To address this, a combination of anti-CD38 monoclonal antibodies and PD-1 inhibitors, together with alternative dosing regimens could be used [158].

Checkpoint signaling, particularly the PD-1/PD-L1 pathway, plays a crucial role in immunosuppression [159]. Increased PD-L1 expression on MM cells can in part be attributed to the production of IFN-γ by BMSCs, which has been demonstrated to trigger T cell apoptosis and inactivity [160–162]. Moreover, PD-L1 positive MM cell lines show increased proliferation due to elevated anti-apoptotic protein levels, and reduced responsiveness to dexamethasone and melphalan [162,163]. A feasible approach may involve the simultaneous administering of bsAbs and immune checkpoint inhibitor mAbs. In preclinical investigations, PD-L1 blockade substantially augmented the anti-myeloma efficacy of cevostamab [26]. Cattaneo et al. [164] developed a bsAb targeting BCMA and PD-L1 which induced killing of up to 75% of target MM cell lines. Research has also demonstrated that BMSCs can protect tumor cells of MM from bsAb-mediated lysis, thus potentially contributing to the inactivity of bsAbs. Counteracting the VLA4 adhesion pathway has been shown to reverse the inhibitory effect of stromal cells on T cell activation [165]. BsAbs were also shown to induce the formation of Tregs to create immunosuppressive conditions. The response to blinatumomab therapy is inversely correlated with the frequency of Tregs in the peripheral blood of treated patients [166]. Strategies to suppress Tregs could therefore alleviate resistance to bsAbs, as demonstrated by pretreatment with cyclophosphamide or fludarabine before blinatumomab administration in such scenarios [167]. Immune-stimulating cytokines such as IL-2, IL-7, IL-15, and IL-21 that can support T-cell proliferation or regulate effector functions are considered to be effective adjuvants for cancer immunotherapy. These recombinant cytokines are currently undergoing extensive testing in combination with immune checkpoint inhibitors and other immunotherapies [168]. While cytokine-based therapies can accompany T-cell immunotherapy, excessive T-cell stimulation can drive activation-induced cell death and hence increase the risk of severe immune-related adverse events such as CRS and ICANS. After conducting functional screening of immune-stimulating cytokines, Casey et al. [169] found that the potential immune-stimulating cytokine IL-21 could induce the release of bsAb-mediated granzyme B and perforin without increasing IFN-γ release, thus making it an ideal partner for bsAb therapy.

6.3 Co-stimulatory Domain

Continuous stimulation of T cell receptor-CD3 signaling in the absence of costimulatory molecules such as CD28 or CD137 was identified as another key factor in the bsAb-induced nonresponse or apoptosis of effector T cells. A tri-specific antibody against CD3, CD28 and CD38 was found to enhance T cell activation and improve the effectiveness of tumor cell targeting. This tri-specific molecule inhibited myeloma growth in a humanized mouse model, stimulated the proliferation of memory/effector T cells, and reduced Treg levels in non-human primates [170].

6.4 In-situ Generation of BsAbs

The therapeutic potential of exogenous bsAbs is hindered by their limited serum half-life and the risk of off-target tumor toxicity. The concept of in-situ bsAb generation aims to circumvent the immunosuppressive TME and eliminate the need for continuous drug administration. Specific approaches for the in-situ generation of bsAbs within the tumor tissue include engineered oncolytic viruses (OVs), transferred autologous tumor specific T cells, and transfected mesenchymal stem cells [171]. OVs represent a promising platform for the delivery of bsAb to tumor sites via their leverage of virus-mediated T-cell recruitment. Yu et al. [172] developed an OV that targets CD3 and EPHA2. This was shown to eliminate infected tumor cells and to induce bystander killing of non-infected cells, thereby demonstrating the potential of bsAb-armied OVs to enhance oncolytic immunotherapy [172]. The combination of CAR-T cells with bsAbs to create autologous tumor-specific T cells is therefore of great interest. Liu et al. [173] created CD19-bsAb transferred T cells that showed superior anti-tumor responses compared to CD19 CAR RNA-transferred T cells. Moreover, due to their inherent migratory capacity, mesenchymal stromal cells have emerged as a “cell platform” for delivering bsAbs to tumor sites in vivo [174].

7. Conclusions

The success of elranatamab and teclistamab has inspired the expansion of bsAbs for the treatment of MM. BsAbs are currently undergoing intensive clinical evaluation for the management of advanced MM patients. However, critical factors for an ideal bsAb include the selec-
tation of optimal antigen, the ability to stimulate effector cells while mitigating excessive immune responses, and overcoming the challenges of the immunosuppressive microenvironment to ensure durability without compromising patient safety. These factors present formidable challenges for scientific researchers. While the journey from laboratory to patient care is still ongoing, the advent of bsAbs as an “off-the-shelf” therapeutic has reshaped the landscape of MM immunotherapy. Future research should focus on strategic combinations with bsAbs to potentially achieve a functional “cure” following frontline treatments.

**Abbreviations**

ASCT, Autologous stem cell transplant; BMSCs, Bone marrow stromal cells; BsAb, Bispecific antibodies; CAR-T, Chimeric antigen receptor T-cell; CR, Complete response; CRS, Cytokine release syndrome; DOR, Duration of response; EMD, Extramedullary disease; IV, Intravenous; mAb, Monoclonal antibodies; MM, Multiple myeloma; MRD, Minimal residual disease; ORR, Objective response rate; OS, Overall response; OVs, Oncolytic viruses; PFS, Progression-free survival; SC, Subcutaneous; TAA, Tumor-associated antigen; TME, Tumor microenvironment; TRAEs, Treatment-related adverse events; VGRP, Very good partial response.

**Author Contributions**

MW and CW: Conceptualization, Writing-original draft, Writing-editing. CS, SL, and YH: Conceptualization, Supervision, Writing-review & editing. JD and HW: draft, Writing-editing. CS, SL, and YH: Conceptualization, Writing-review & editing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

**Ethics Approval and Consent to Participate**

Not applicable.

**Acknowledgment**

Not applicable.

**Funding**

This research received no external funding.

**Conflict of Interest**

The authors declare no conflict of interest.

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