Clinical updates of B-cell maturation antigen-targeted therapy in multiple myeloma (MM) and relapsed/refractory MM (Review)

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Abstract. Despite significant progress in managing multiple myeloma (MM) in recent years, certain patients still have a short duration of therapeutic response, often relapsing within 18 months. These patients typically have high-risk genetic mutations and may show little to no response to current treatments, highlighting the need for further exploration of optimal therapeutic targets for MM. B-cell maturation antigen (BCMA), highly expressed in mature B lymphocytes and plasma cells and upregulated in MM, is a promising therapeutic target. Various BCMA-targeted strategies, including antibody-drug conjugates, bispecific T-cell engagers and chimeric antigen receptor T-cell therapy, are under clinical evaluation to optimize efficacy and safety. This review summarizes the latest clinical updates on these strategies, highlights their effectiveness in MM and relapsed/refractory MM and provides future perspectives and recommendations for overcoming current challenges.

Contents

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1. Introduction

Multiple myeloma (MM) represents a hematologic neoplasm characterized by the presence of aberrant clonal plasma cells within the bone marrow environment. According to an annual report from the American Cancer Society for 2023, an approximate total of 35,730 novel cases of MM were predicted to be diagnosed in the US, alongside a count of 12,590 fatalities attributed to this condition (1). Consequently, a profound comprehension of the intricate mechanisms underlying the pathogenesis of MM is of significant importance.

Currently, treatment of patients newly diagnosed with MM starts with induction therapy, followed by consolidation therapy and finally maintenance therapy for those who are suitable for hematopoietic stem cell transplantation (2-6). The existing therapeutic approach during the induction therapy phase involves the consideration of the impact of lenalidomide on stem cell drug toxicity and the hepatotoxicity associated with high-dose chemotherapy in the elderly demographic. The incorporation of B-cell maturation antigen (BCMA) antibodies into this phase of treatment prompts an inquiry into the potential enhancement of accessibility to autologous stem cell transplantation consolidation within this patient population (2,7,8). In consolidation treatment, stratified treatment is used to evaluate whether the patients are suitable for autologous stem cell transplantation according to their age, scores of the Eastern Cooperative Oncology Group and the state of complications. Among them, the combination of bortezomib, lenalidomide and dexamethasone (VRD) has been selected as the preferred induction regimen if the condition of primary MM allowed, and hematopoietic stem cell collection was performed within 4 cycles to reduce the

toxicity of lenalidomide on hematopoietic stem cells and its effect on later implantation (9,10). In addition, there are certain reports addressing the potential to improve complete response (CR) rates and achieve profound remissions through the combination of BCMA-targeted agents with proteasome inhibitors and immunomodulatory drugs. It is noteworthy that BCMA-targeted therapeutics are presently predominantly used in patients with MM who have relapsed, are refractory or have relapsed following multiple lines of therapy (11). During the maintenance phase of MM treatment, the National Comprehensive Cancer Network and European Society for Medical Oncology guidelines recommend lenalidomide as the preferred maintenance therapy for MM, but certain patients are insensitive or intolerant to it (11,12). In such cases, alternative therapies are essential to maintain therapeutic efficacy (13).

BCMA is mostly expressed on mature B lymphocytes, with its overexpression and activation associated with human MM progression (14). BCMA is a transmembrane glycoprotein of type III, with 184 amino acids and possessing a molecular weight of 20.2 kDa, featuring an extracellular N-terminus with a conserved 6-cysteine motif. This glycoprotein is categorized as a constituent of the necrosis factor family (10,15,16). BCMA interacts with the following tumor necrosis factors (TNF) family members: B-cell activator of the TNF family (BAFF) and a proliferation-inducing ligand (APRIL) to induce plasma-cell survival. The progression of human MM is associated with an increase in the expression of BAFF and APRIL in serum instead of the bone marrow microenvironment. Upon binding to APRIL or BAFF, BCMA influences B cells by promoting their proliferation, survival, differentiation and maturation into plasma cells; this modulation is essential for the prolonged survival of plasma cells (17,18). In the context of MM, both BCMA mRNA levels and the abundance of BCMA protein are markedly elevated when compared to normal plasma cells (19). This substantial upregulation of BCMA represents a pivotal factor in the initiation and progression of MM, making it an essential target for treatment (20). Drug resistance in MM arises through various mechanisms, including genetic and cellular changes. Polymorphisms in multidrug resistance genes and the overexpression of P-glycoprotein in MM cells contribute to resistance (21). Alterations in the tumor microenvironment, such as increased cell adhesion and activation of anti-apoptotic cytokine pathways like JAK/STAT and PI3K/AKT, also play a significant role. Clonal evolution, including the hyperexpression of proteasome 26S subunit ubiquitin receptor, non-ATPase 4 due to chromosome 1q21 amplification, and the post-treatment accumulation of $CD34^{+}CD138^{+}B7\text{-}H1^{+}CD19^{-}$ plasma cells, further contributes to resistance. Additionally, the dysregulation of various microRNAs impacts MM cell survival, the cell cycle and the microenvironment, leading to resistance to therapies such as bortezomib. Furthermore, programmed cell death 1 (PD-1) is upregulated on T cells in patients with MM, while PD-1 ligand 1 expression is elevated on MM cells, further contributing to immune evasion and resistance (5,15,16,20,22).

A survey commissioned by the MM Patients Advocacy Group revealed that 92% of patients with MM were aware of BCMA-targeted therapies. The top three concerns include the assessment of efficacy, consideration of potential side effects and evaluation of eligibility criteria. Patients expressed their willingness to embrace novel drugs and undergo monitoring for potential side effects. This finding underscores the open-mindedness of patients with MM towards adopting innovative treatment modalities (21).

Currently, BCMA has emerged as a promising candidate for diverse therapeutic interventions, encompassing targeted therapies, and has additionally demonstrated potential as a prognostic biomarker. The multifaceted roles played by BCMA underscore its significance in the pathogenesis and clinical management of MM. For instance, Dhakal *et al* (23) conducted a phase 3, randomized, controlled trial on patients with 1-3 prior lines of therapy who were refractory to lenalidomide, targeting BCMA. The trial yielded promising results, with a CR rate of ≥73.1% and an overall response of 84.6%, highlighting the potential efficacy of BCMA-targeted therapies in a specific subset of patients with MM and underscores the significance of ongoing research and clinical trials in this area (14,24).

2. BCMA

As a biomarker. The National Institute of Health defines a biomarker as an objectively measured indicator of biological processes, whether normal, pathogenic or in response to a therapeutic agent (25,26). Biomarkers, found in body fluids or tissues, can be genomic, transcriptomic, proteomic or clinicopathologic, and serve diagnostic, prognostic or predictive purposes (27,28). Due to the small portion of the MM plasma cells, more reliable biomarkers that can be widely used are needed to guide treatment decisions (29).

Flow cytometry is a crucial tool for diagnosing MM by determining the proportion of monoclonal plasma cells in bone marrow and common markers including CD38, CD138 and CD56 are used to distinguish neoplastic myeloma cells from reactive plasma cells in clinical practice (30). However, these markers have separate limitations: CD138 degrades with temperature and time, CD38 can be influenced by other diseases or medications and CD56 is a non-specific marker for MM (30-32). BCMA is highly expressed on malignant plasma cells and high expression of BCMA in serum is associated with the progression and the objective response rate (ORR) in patients with MM and mouse models (33,34). Numerous studies have screened the diagnostic utility of BCMA, predicting treatment responses and assessing prognosis. Notably, a reduction in soluble BCMA (sBCMA) has been consistently observed in various clinical trials, correlating with an improved ORR (33). Furthermore, BCMA antigen is overexpressed in abnormal plasma cells and it is stable and not easily degraded by temperature (35,36). In addition, BCMA shows consistent expression in newly diagnosed and relapsed/refractory (R/R) MM, suggesting its potential as a biomarker across disease stages (9).

Monitoring serum sBCMA levels and minimal residual disease (MRD) levels of BCMA expression by flow cytometry also provides valuable insight (37). Lower sBCMA levels indicate effective treatment, while higher levels are associated with the tumor burden (38,39). With a short half-life of 24-26 h, sBCMA quickly reflects treatment effects, making it a sensitive marker for monitoring disease status. This offers an advantage over traditional M-protein monitoring, whose serum

half-life typically spans three to four weeks (40,41). In addition, anti-BCMA antibody treatments are less prone to immune escape, making sBCMA a reliable tumor marker (9,42).

As a prognostic indicator. Prognostic assessment tools for MM include ISS staging, R-ISS staging, the 2014 IMWG criteria and Mayo staging, alongside genetic analysis via fluorescence *in situ* hybridization (FISH) or the detection of complex karyotypes via high-resolution chromosome examination (43). In a cohort comprising 36 MM patient samples, a hybridization technique was employed using three distinct probes designed for chromosome 13q (43-45). The outcomes of this analysis indicated that the utilization of FISH studies indicated not only the translocation of chromosome 14q32 but also 17p13 yielded notably meaningful findings during the clinical follow-up of patients with MM. These results confirmed the precise detection of chromosome mutation in patients with MM with FISH (38,46,47). However, these methods can be costly, time-consuming and require specialized expertise, highlighting the need for novel prognostic markers which can be easily accessed.

sBCMA has emerged as a valuable predictor of progression-free survival (PFS) in patients with MM (48). High sBCMA levels before treatment are linked to poorer clinical outcomes and elevated levels during early treatment phases suggest an unfavorable prognosis (33,49). Various methodologies employed for the detection of BCMA in serum may contribute to the observed association between sBCMA levels and clinical prognosis (50). sBCMA, shed from MM cells, indicates tumor burden and quickly reflects changes in response to treatment, offering a rapid prognostic tool (20,41).

BCMA-targeted therapies do not interfere with sBCMA detection and BCMA can be used in high-throughput flow cytometry to assess MRD. This method is currently more reliable for disease monitoring than next-generation sequencing, though there is no consensus on the definition of a negative MRD test (51).

As a target. Given the established efficacy of BCMA-targeted therapy, numerous patients now have access to innovative drugs for combatting R/R MM. Certain diagnostic tools and biomarkers have demonstrated drug-targeted value, and the advent of flow cytometry and sequencing technologies facilitates the monitoring of MRD (50). These advances enable the identification of specific high-risk groups and patients with R/R MM. One of the primary objectives in the design of BCMA-targeting drugs is to address these high-risk groups and improve the prognosis of MM and R/R MM and the ultimate goal is to delay disease recurrence and progression, with the intention of extending overall survival (OS). Presently, there exist three predominant strategies for the treatment of R/R MM and MM targeting BCMA including monoclonal antibodies, antibody-drug conjugates and emerging therapies.

Monoclonal antibodies. These agents target antigens upregulated in MM cells, engaging immune mechanisms such as complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) (52). For instance, GSK2857916, a glycosylated IgG1 BCMA antibody drug (53,54), which enhances BCMA-targeted therapy efficacy by improving ADCC through stronger binding to the FC gamma receptor (FcgR) IIIa/CD16a receptor, has shown efficacy in phase 2 trials with an ORR of 33%. Its cytotoxic payload was activated upon targeted delivery and was demonstrated to be more potent compared to non-targeted drugs; its hydrolysis-resistant linker ensures stability and efficient transport (16,55).

Furthermore, GSK2857916 induces cell cycle arrest and apoptosis in MM cells, triggers ADCC and ADCP through interactions with natural killer (NK) cells, peripheral blood mononuclear cells and macrophages, competes with BAFF and APRIL to reduce NF-κB activation and diminishes NF-κB pathway support for MM-cell proliferation and drug resistance (52,53,56,57) (Fig. 1A).

Antibody-drug conjugates (ADCs). ADCs consist of monoclonal antibodies that can specifically target antigens on tumor cells. Once ADCs bind to the surface antigens expressed on tumor cells, toxic payloads are released from ADCs, resulting in the microtubule inhibition or DNA damage in the tumor cells. AMG224 and MEDI2228 are examples of ADCs targeting BCMA. AMG224 achieved an ORR of 23% in phase 1 trials of patients with MM and R/R MM with lower sBCMA (36,38,58).

MEDI2228 is a fully human ADC targeting BCMA, linked to a DNA cross-linking pyrrolobenzodiazepine dimer through a protease-cleavable linker, and it synergizes with DNA damage response inhibitors to induce apoptotic cell death via DNA cross-link formation (59). Clinical studies have shown its superior efficacy compared to monomethyl myricin F analogs, particularly in the presence of elevated sBCMA levels, with ongoing Phase 1 trials assessing its use as monotherapy in R/R MM conditions with the mechanism of interferon (IFN)-stimulated gene enrichment following the DNA damage-ATM/ATR-checkpoint kinase 1/2 pathway (60,61).

MEDI2228 also activates the IFN-regulated innate immune response through the cyclic GMP-AMP synthase-stimulator of interferon genes-TANK binding kinase 1-interferon regulatory factors (IRF)3 and signal transducer and activator of transcription 1-IRF1 pathways in MM cells, demonstrating efficacy against both proliferating and quiescent MM cells *in vitro*, though it is less effective against BCMA-negative cells. In murine models, a single low-dose intravenous administration of HDP-101, an analogous ADC, induced tumor regression and achieved sustained complete remission (61) (Fig. 1B).

Emerging therapies. There are also emerging therapies targeting BCMA to enhance clinical outcomes. SEA-BCMA is a humanized IgG1 monoclonal antibody targeting BCMA, showing promising early clinical results with an ORR of 30%. It inhibits BCMA-mediated pro-survival signaling, enhances ADCC and phagocytosis and has demonstrated potential for durable anti-tumor activity, particularly in patients with advanced, heavily pretreated MM (59,62). Preliminary data from the SGN-BCMA-001 (NCT03582033) trial support its favorable safety profile and suggest potential for synergistic combinations. Despite the advantages over CAR-T therapy, such as accessibility and applicability to elderly patients, BCMA-targeted therapies may pose toxic side effects and economic burdens with prolonged use (62,63) (Fig. 1C). However, it is essential to acknowledge that these therapies may entail potential toxic side effects and their efficacy when used

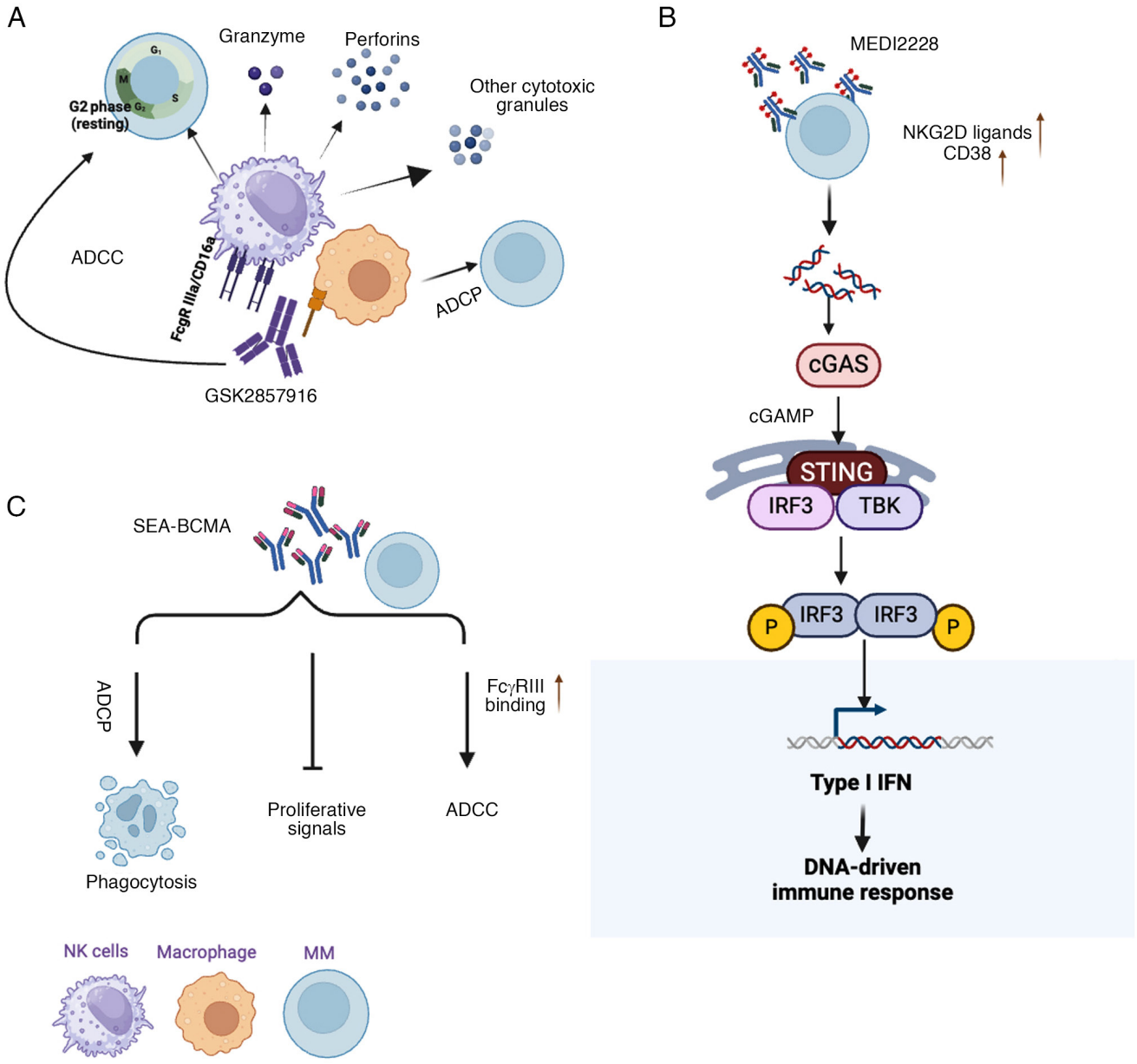

Figure 1. Mechanisms of action of three BCMA-target drugs. (A) GSK2857916 induces MM-cell death via ADCC and ADCP: Enhances efficacy by increasing NMM NMN pathway. (B) SEA-BCMA inhibits BCMA through three primary mechanisms: Blocking pro-survival signaling, enhancing ADCC and promoting phagocytosis. triggers ADCP through interactions with macrophages. (C) MEDI2228 activates the IFN-regulated innate immune response via the cGAS-STING-TBK1-IRF3 NMO MM, multiple myeloma; NK, natural killer; BCMA, B-cell maturation antigen; ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; TBK1, TANK-binding kinase-1; IRF3, interferon regulatory factor-3.

as single agents tends to be moderately effective. In addition, the prolonged use of these drugs may impose a considerable economic burden.

3. BCMA-targeting strategies to modulate the immune microenvironment (IME)

Having gained insight into the biological characteristics of BCMA and its involvement in the pathways driving tumor progression, this next chapter will delve into ongoing clinical trials focusing on drugs that influence the IME to extend survival through administration of the optimal doses with mitigated adverse effects and maximal survival (8).

Bispecific T-cell engagers (BiTEs). BiTEs represent a specialized form of targeted immunotherapy that operates independently of major histocompatibility complex restriction but the requirement for intact antigen-presenting cell function (64). These BiTEs facilitate T cell-mediated cytotoxicity by directly binding T cells to surface antigens present on tumor cells. Upon interaction with both the target tumor cell and T-cell lymphocyte, BiTEs initiate the activation of the T-cell receptor and subsequent downstream signaling events (65). BiTEs are designed with one or more high-affinity domains capable of binding the target protein on the tumor cell and a single lower-affinity domain that binds a protein on immune cells, particularly CD3 on T cells (64,65) (Fig. 2). Certain BiTEs

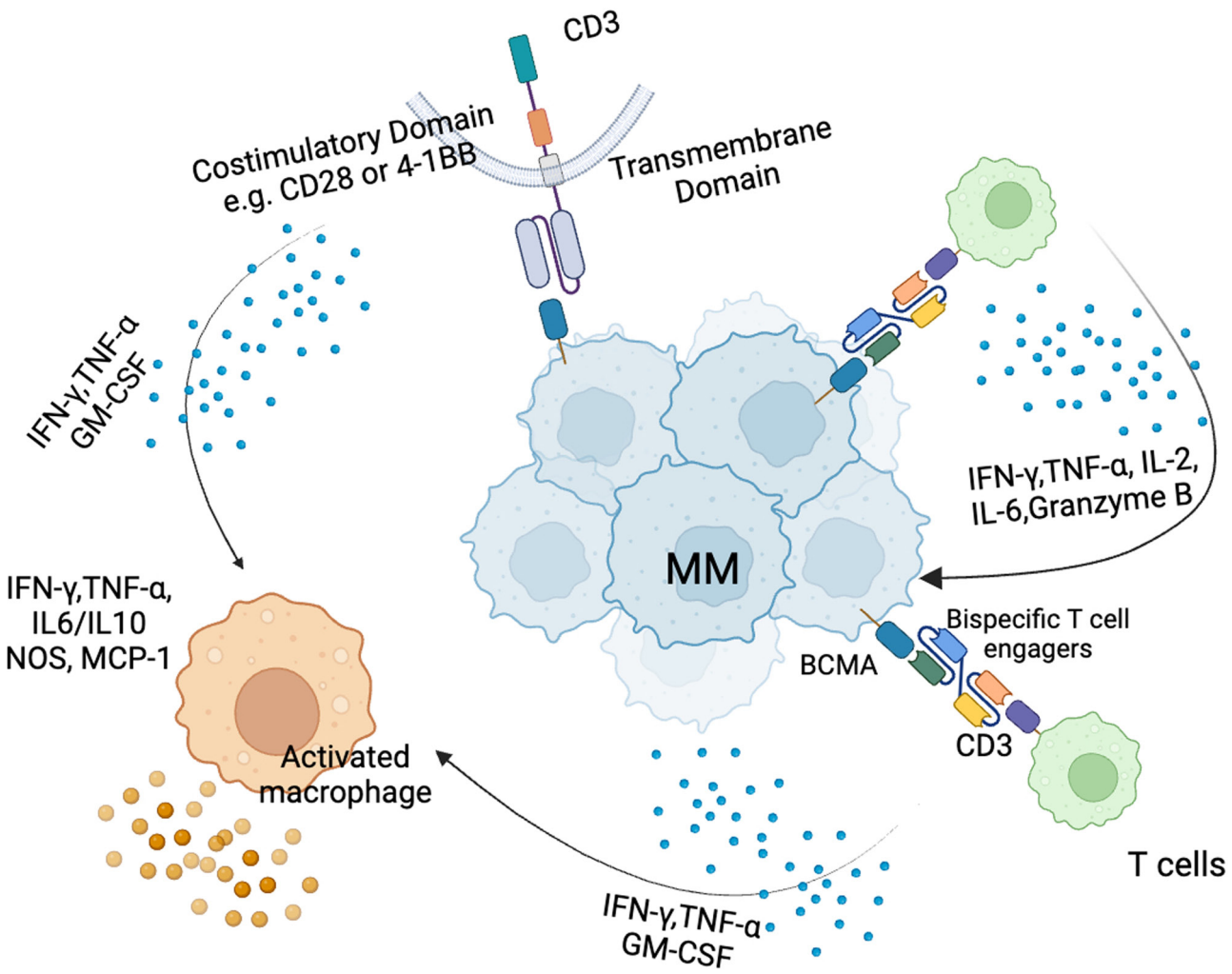

Figure 2. Mechanism of action of bispecific T-cell engagers and CAR-T cells in MM. Upon binding to BCMA expressed on MM cells, bispecific T cells release cytokines such as IFN-γ and TNF-α, which can further activate macrophages. These activated macrophages, also influenced by CAR T cells, release additional cytokines (e.g., IFN-γ, TNF-α, IL-6 and IL-10) into the TIME, thereby reshaping the TIME and enhancing the anti-tumor response. CAR, chimeric antigen receptor; MM, multiple myeloma; BCMA, B-cell maturation antigen; TIME, tumor immune microenvironment; IFN, interferon; TNF, tumor necrosis factor; IL, interleukin 2.

also target other T-cell receptors, such as CD16, NKG2D and, notably, G-protein coupled receptor C family 5D (GPRC5D), which is a non-BCMA-directed T-cell engager. GPRC5D is highly expressed on the surface of plasma cells (66-68).

This section reviews the latest clinical trial results of BiTEs targeting BCMA in the treatment of MM, highlighting their potential to improve outcomes for patients with R/RMM, along with their advantages and disadvantages (Table I) (69).

Teclistamab. Teclistamab, a BCMA-CD3 bispecific antibody, is effective in treating R/R MM and can be administered intravenously (IV) or subcutaneously (S.C.). In the NCT03145181 trial, teclistamab achieved an ORR of 65% in 165 patients, with responses showing durability and an increasing depth over time (70). In addition, in the phase 3 trial sponsored by Janssen Research Development, conducted in patients with a median age of 64 years who had received more than three prior therapies, an ORR of 64% was observed, with 30% achieving a CR or partial response (PR) (63). The reduction in sBCMA levels correlated with treatment response, indicating its potential as a biomarker.

A reduction of 82% in BCMA was observed in 27 patients who had achieved a stringent CR (sCR), while an 87% reduction was noted in the 8 patients exhibiting a CR. Furthermore, a reduction of 90% was identified in 34 patients demonstrating a very good PR (VGPR) (63,70). The ongoing phase 3 NCT05083169 trial, launched by Janssen Research, is evaluating the efficacy and safety of teclistamab in combination with daratumumab, compared to other treatment options in patients with R/R MM. This research provides valuable insights into the optimal treatment for this patient population. The results demonstrate substantial clinical activity of teclistamab in heavily pretreated R/R MM, favorably comparing to existing therapies, including CAR-T. While side effects such as cytokine release syndrome (CRS) and neutropenia were observed, CRS events were generally mild, with few grade 3 and no grade 4 occurrences. The lower-grade CRS profile with teclistamab supports its potential for outpatient administration. Although toxic effects were common, they were mainly low-grade and reversible, indicating a significant clinical benefit for a broader patient population (71).

Table I. Summary of clinical trials for bispecific T-cell engagers targeting BCMA.

Product name	Antigen target	Clincial phase	Condition	Patients, n	ORR, %	ClinicalTrials ID	Sponsor
Teclistamab	BCMA	Phase 1-2 study	R/R MM	165	ORR, 65; CR, 30	NCT03145181	Johnson & Johnson
Teclistamab	BCMA	Phase 3	R/R MM	560	Ongoing	NCT05083169	Johnson & Johnson
REGN5428	BCMA	Phase 1	R/R MM	252	ORR, 60; CR, 31.3	NCT03761108	Regeneron Pharmaceuticals
Elranatamab	BCMA	Phase 1	R/R MM	123	ORR, 68; CR, 38.2	NCT03269136	Pfizer
ABBV-383	BCMA	Phase 1	R/R MM	124	ORR, 68; CR, N/A	NCT03933735	TeneoOne Inc.
AMG 701	BCMA	Phase 1	R/R MM	75	At a dose of 9 mg: ORR, 83; CR, N/A	NCT03287908	Amgen
CC93269	BCMA	Phase 1	R/R MM	70	ORR, 83.3; CR, N/A; CR, N/A	NCT03486067	Celgene

BCMA, B-cell maturation antigen; ORR, objective response rate; R/R MM, relapsed/refractive multiple myeloma.

REGN5428. REGN5428, a bispecific antibody targeting BCMA and CD3, was evaluated in a Phase 1 clinical trial (NCT03761108) using a 4+3 dose-escalation design, with IV weekly administration followed by biweekly maintenance. At the highest dose level, the trial achieved an ORR of 60% in 252 patients with a median age of 66 years. Among the participants, 81.3% achieved a VGPR, 31.3% reached a CR and 43.8% maintained remission for over four months (72).

Results from Phase 2 studies released this year focused on dose optimization between 50 and 200 mg. The results revealed that patients treated with 200 mg reached a higher efficacy than those receiving 50 mg, with an ORR of 64 and 50%, respectively. Of note, the 200-mg dose also correlated with fewer AEs, with 95% of patients experiencing adverse events (AEs) vs. 100% in the 50-mg group. Common treatment-emergent AEs included CRS in 37% of the 200-mg group (1% Grade 3) and 53% of the 50-mg group (2% Grade 3). Fatigue occurred in 32% of the 200-mg group and 33% of the 50-mg group, with no severe cases. Anemia was reported in 28% of the 200-mg group (24% severe) and 40% of the 50-mg group (36% severe) (72-74). This clinical trial has recently concluded enrollment and is currently in the follow-up phase.

Recently, an additional open-label, multi-cohort clinical trial (NCT05137054) was initiated to evaluate the efficacy of REGN5458 in conjunction with anti-CD38 antibody, immunomodulatory drug (IMiD) and 1 proteasome inhibitor (PI) in patients with R/R MM. Results indicate that when combining REGN5428 with IMiDs, PIs and anti-CD38 agents, the higher concentration of 200 mg may be a more effective option for treating R/R MM (74).

Elranatamab. Elranatamab, also known as PF-06863135, is a humanized IgG2-type bispecific antibody that targets BCMA and CD3. It can be administered weekly either IV or S.C. Administration leads to slow absorption, with a half-life of 3 to 7 days (75-77). In the phase I NCT03269136 trial, Elranatamab, a monoclonal antibody for treating R/R MM, was administered at varying concentrations. Among those receiving S.C. monotherapy, 55 patients were treated at efficacious dose levels (≥215 μg/kg), while 10 patients treated with sub-efficacious dose levels (80 or 130 μg/kg) did not achieve an IMWG-confirmed PR or better. With a median follow-up of 12 months, the ORR was 63.6, and 38.2% of patients achieved a CR or better, with no grade ≥3 AEs observed (76,77). These results highlight how immunotherapeutic approaches have expanded treatment options for patients with R/R MM with a higher dose, underscoring the importance of therapy to enhance efficacy while minimizing toxicity for each patient. In the Phase II clinical trial (NCT04649359), 123 patients who had previously undergone non-BCMA-targeted therapies were enrolled. Participants received S.C. elranatamab at a dose of 76 mg once weekly in 28-day cycles, following two step-up priming doses of 12 and 32 mg administered on day 1 and 4 of cycle 1, respectively. A CR or better was observed in 35.0% of the patients, while a VGPR or better was achieved in 56.1% of the cohort. The easy assessment of elranatamab posits it as a viable alternative option to CAR-T-cell therapy. Further clinical trials should be performed to observe the AEs and efficacy of elranatamab given at a biweekly dose, aiming for it to maintain its high efficacy while minimizing AEs (77,78).

ABBV-383. ABBV-383, a BCMA x CD3 bispecific T-cell-redirecting antibody, is administered IV once every three weeks in patients with R/RMM, showing low AEs. In the NCT03933735 Phase I trial, which utilized a 3+3 design with backfilling for dose escalation, the treatment demonstrated promising outcomes (79). The trial showed an impressive 68% ORR in patients receiving doses of 40 mg or higher. As a monotherapy, ABBV-383 demonstrated significant efficacy at both 40- and 60-mg doses, with a median PFS of 13.7 and 11.2 months, respectively. The 12-month duration of response (DOR) was 70% at 40 mg and 66% at 60 mg, with the median DOR not yet reached in patients achieving a CR or better (80,81). However, the ORR at 60 mg was slightly lower at 59%. Hematologic treatment-emergent AEs (TEAEs) were mainly neutropenia (37%) and anemia (29%), while non-hematologic TEAEs included CRS (57%) and fatigue (30%) (82,83). ABBV-383 administration at doses of 20, 40 and 60 mg can led to a rapid but transient induction of key proinflammatory cytokines (IL-6, IL-8, IFN-γ and TNF-α) and a gradual decrease in sBCMA levels, correlating with the therapeutic response. In addition, ABBV-383 promoted T-cell activation and proliferation, as indicated by increased expression of CD69 and Ki67 markers on peripheral CD4 and CD8 T cells in evaluable patients. These findings highlight ABBV-383's significant potential to prolong OS in patients with R/R MM even with low doses (<60 mg) (81).

Furthermore, it is worth noting that a dose of 40 or 60 mg of ABBV-383 every three weeks has been selected for further exploration as the optimal regimen. The low-dosing frequency and off-the-shelf availability make ABBV-383 a convenient option for patients with R/R MM compared to CAR-T therapy. In addition, its high efficacy is comparable to that of ADC belantamab mafodotin and CAR-T-cell therapies, which is 32 and 61.5-97%, respectively (82).

AMG 701. AMG 701 represents a bispecific single-chain variable fragment (scFv) antibody that incorporates a hexahistidine tag for identification and purification. Its mode of administration involves IV infusions administered weekly, organized within 4-week cycles (84). The Phase I clinical trial aimed to evaluate the safety, tolerability and anti-myeloma activity of AMG701, as well as to estimate a biologically active dose. The results indicate that the response to AMG701 is dose-dependent. At doses ranging from 3 to 12 mg, the response rate was 36% (16 out of 45 patients), while with an earlier dose escalation to 9 mg, the response rate increased significantly to 83%, including 3 PRs and 2 VGPRs. While the underlying mechanisms require further exploration, studies in a mouse model showed that AMG701 increases survival, potentially through the induction of PD-1 expression on T cells. Furthermore, combining AMG701 with a PD-1-blocking antibody enhanced its efficacy, alongside increased concentrations of cytokines, such as IFN-γ and IL-2. These findings suggest a promising potential for combining anti-PD-1 therapy with AMG701(83,84).

CC-93269. CC-93269 is an asymmetric 2-arm humanized IgG T-cell engager that binds bivalently to BCMA and monovalently to CD3ε in a 2+1 format. It can induce interaction between T cells and BCMA-expressing myeloma cells and induces T-cell receptor/CD3 cross-linking leading to T-cell activation, and release of proinflammatory cytokines and cytolytic enzymes, resulting in MM-cell death (NCT03486067) (16,85).

The initial report released in 2019, involving 19 patients with a median age of 64 years who were resistant to their last line of treatment, aimed to assess the safety and anti-tumor response of CC-93269 at doses ranging from 0.15 to 10 mg. Among the 12 patients treated with ≥6 mg in Cycle 1, 10 achieved a PR or better, yielding an ORR of 83.3%. This included 7 patients (58.3%) who achieved a VGPR or better and 4 patients (33.3%) who attained an sCR; 9 patients (75.0%) also achieved MRD negativity (86).

A subsequent clinical trial report from 2022 for measuring the efficacy of CC-93269, which included 70 patients, indicated that 39% (27/70) achieved an objective response, with a median PFS of 13.3 weeks. All CRS events were limited to grade 1 (45%) or grade 2 (9%). Notably, none of the patients discontinued treatment due to AEs and no treatment-related deaths occurred. At the 30-mg target dose, observed trough concentrations by Cycle 2 Day 1, the predicted levels required for efficacy were exceeded (85-87). The number of patients in the clinical trial for CC-93269 was limited and additional participants are needed to draw broader conclusions.

4. CAR-T BCMA drugs have shown promising efficacy in the treatment of R/R MM

Over 20 CAR-T products targeting BCMA are currently in clinical trials, with variations in design, BCMA epitopes, co-stimulation thresholds and viral vectors leading to differences in efficacy and challenges in production time and cost (88,89).

CAR-T therapy is the most effective BCMA-targeted treatment for R/R MM, generally achieving a 50-93% ORR in patients who have relapsed after three or more lines of therapy; the structure and clinical efficacy of major second-generation CAR-T-cell therapies are summarized in Table II (16,90,91). The therapy activates T-cells' tumor-killing abilities through specific antigen recognition and co-stimulatory signals, but the associated toxicities, including CRS, immune effector cell-associated neurotoxicity syndrome (ICANS), hematologic toxicity, infection and tumor lysis syndrome, limit its application (Fig. 2). CRS, triggered by cytokine release, affects >60% of patients, with the severity influenced by disease type, CAR-T dose and co-stimulatory molecules, while ICANS presents with neurological symptoms and requires similar treatment (91-93). Hematological toxicity, mainly due to lymphocyte depletion and off-target effects, increases infection and bleeding risks, which can be managed with transfusions and growth factors (94).

In this review, recent advances in clinical trials related to CAR-T therapies targeting BCMA were summarized and the future directions for these drugs were outlined (Table III).

bb2121. b2121, also known as Idecabtagene vicleucel, a CAR T-cell therapy targeting BCMA, shows significant potential in the treatment of MM. It is the first CAR-T-cell therapy approved for treating R/R MM after four or more prior therapies. bb2121 shows reduced antigen-independent signaling and strong *in vitro* cytotoxicity against myeloma cells with varying

Table II. Overview of ongoing/completed next-generation CAR-T cell therapy targeting B-cell maturation antigen.

Product name	ScFv	Costimulatory molecule	Platform of virus	Outcome, %	CRS, %	Clinical trial no.
bb2121	Rat	4-1BB	Lentivirus	ORR, 85; CR, 45	76	NCT02658929
bb21217	Rat	4-1BB	Lentivirus	ORR, 83; CR, 25	67	NCT03274219
BRD015	Rat	CD28	Lentivirus	ORR, 93; CR, 73	76	ChiCTR-OPC-16009113
LCAR-B38M	UA	4-1BB	Lentivirus	ORR, 88; CR, 68	89	NCT03090659
MCARH171	Human	4-1BB	Retrovirus	ORR, 64; CR, 0	60	NCT03070327
CT103A	human	4-1BB	Lentivirus	ORR, 100; CR, 70	94	ChiCTR 1800018137)
JCARH125	Human	4-1BB	Lentivirus	ORR, 82; CR, 27	80	NCT03430011
FCARH143	Human	4-1BB	Lentivirus	ORR, 100; CR, 36	91	NCT03338972

CAR, chimeric antigen receptor; ORR, objective response rate; CR, complete response; ScFv, single-chain variable fragment; CRS, cytokine release syndrome, CAR, chimeric antigen receptor.

Table III. Summary of clinical trials for CAR-T cells targeting BCMA.

Product name	Antigen target	Clincial phase	Condition	Patients, n	Response, %	Clinical Trials ID	Sponsor
bb2121	BCMA	Phase 1	R/R MM	33	ORR, 85; CR, 45	NCT02658929	Celgene
CT103A	BCMA	Phase 1b/2	R/R MM	18	ORR, 96 CR, 74.3	NCT05066646	Nanjing IASO Biotechnology Co., Ltd.
GC012F	BCMA and CD19	Phase I	R/R MM	29	ORR, 93; CR, 82.8	NCT04236011; NCT04182581	Gracell Biotechnologies
MCARH171	BCMA	Phase 1	R/R MM	11	ORR, 64; CR, N/A	NCT03070327	Memorial Sloan Kettering Cancer Center

CAR, chimeric antigen receptor; R/R MM, relapsed/refractive multiple myeloma; BCMA, B-cell maturation antigen; ORR, objective response rate; CR, complete response.

BCMA expression. Previously, in an *in vivo* NOD scid gamma (NSG) mouse model of human MM, bb2121 achieved rapid and sustained tumor elimination (13,35).

In the Phase I clinical trial (NCT02658929), which included 33 patients with MM who received CAR-T-cell infusions ranging from 10-800x10^6 in the dose-escalation phase and 150 or 450x10^6 in the expansion phase, an impressive ORR of 85% was achieved, with 9 patients attaining CR without any relapse. Patients who received >150x10^6 demonstrated a better response rate (35).

Additionally, the clearance of bone marrow plasma cells occurs rapidly, typically within one month, and the incidence of AEs is low, primarily restricted to grade 1 or 2. Importantly, the efficacy of the treatment appears to be independent of BCMA expression, as both high and low expression levels result in similarly high response rates, indicating its potential applicability for a broad range of MMs. However, there are limitations to consider. The small sample size limits the generalizability of the findings and future studies should involve a larger patient cohort to better evaluate the treatment's efficacy (35).

In the subsequent Phase II clinical trial conducted in Japanese patients with R/R MM, an impressive ORR of 89% was achieved with a median follow-up of 12.9 months. The treatment was also associated with low AEs: Predominantly grade 1 or 2. Notably, the regimen involving 450x10^6 CAR-positive T cells offered the potential for a treatment-free period in this challenging patient population. However, with only 9 patients included to date, further studies with a larger cohort are needed to validate these efficacy findings (95).

CT103A. CT103A constitutes a fully human CAR-T-cell product designed to target BCMA. Clinical investigations of CT103A include a phase 1, single-arm, open-label trial conducted at Tongji Hospital in China (NCT05066646). The study enrolled 18 patients with R/R MM, all of whom had received a minimum of three prior lines, and the follow-up was 394 days. Patients with MM resistant to CAR-T-cell

therapy still benefited from CT103A, achieving an ORR of 98% with low AEs including no observed immune effector cell-associated neurotoxicity syndrome. After 1 year, the PFS rate was 58.3% for all cohorts and 79.1% for the patients without extramedullary myeloma. Furthermore, even at the lower dosage levels (1 and $3x10^6$ CAR-T cells/kg), CT103A demonstrated continued activity and effectiveness with minimal side effects (95,96).

Regarding safety outcomes, the predominant late AEs observed 8 weeks post-CAR-T-cell infusion were hematologic toxicities, notably leukopenia and neutropenia. In addition, increasing the number of patients in the study would strengthen the remarkably high-efficacy results (97).

GC012F. GC012F is a dual-targeting CAR-T-cell therapy that targets both BCMA and CD19. It was developed using the innovative FasTCAR-T platform within 22-36 h (98).

The overall response rates were 93.1% (27/29) and most AEs were grade 2 or lower (79.3%), with only 6.9% of patients experiencing grade 3 CRS. GC012F persisted for a median of 410 days (range, 51-1,183 days) and notably remained detectable in 79.3% of patients at 6 months and in 55.2% at 12 months post-infusion. sBCMA plasma levels began to decline by day 4 in 80% of patients, decreased sharply by day 10 in all patients and reached minimal levels from 30 to 60 days post-infusion in all patients (NCT04236011; NCT04182581) (99).

These robust response rates and extended durations of response underscore the promising therapeutic efficacy of the studied cohort but more R/R MM patients should be included for future exploration (98).

MCARH171. MCARH171, a type of next-generation anti-BCMA CAR-T cell, was investigated in patients with R/R MM (100). A total of 11 patients with R/R MM were treated, with a median of six prior therapy lines, achieving a 64% ORR and a median response duration of 106 days in the NCT03070327 clinical trial. Peak expansion and persistence of MCARH171, along with durable clinical responses, were dose-dependent. Patients treated with $\leq 150x10^6$ CAR-T cells had lower peak expansion in their peripheral blood compared to those receiving $\geq 450x10^6$ CAR-T cells, showing promising efficacy at higher doses. Peak expansion was associated with response durability, independent of the dose level (91,100). The clinical trial of this drug is constrained by a short follow-up duration and a limited number of participants. However, while the drug shows significant efficacy in treating R/R MM, its performance is not comparable to that of other CAR-T therapies (100).

5. Conclusion and future perspective

The efficacy of BCMA as a therapeutic target in MM or R/R MM has been demonstrated for common ADC drugs, bispecific antibody T-cell activators and CAR-T-cell therapy. Overall, CAR-T cell therapy and BiTEs activators were more efficacious than ADC drugs alone, reflecting the superiority of antitumor immunotherapy over traditional single-target ADC drugs. In addition, non-BCMA-targeted CAR-T-cell therapies have shown promising results, further contributing to options against the disease. CAR-T cells can specifically target MM cells, either through a single target or dual targets (e.g., BCMA and CD19), and a single dose has been shown to provide sustained efficacy for >12 months with lower AEs. Among the therapies, CAR-T-cell therapy demonstrates the highest therapeutic efficacy on average. However, it is also the most expensive compared to other treatments, including ADCs and BiTEs. In addition, the low administration frequency of certain BiTEs, such as ABBV-383, which is given every three weeks, offers an economic advantage by potentially reducing the financial burden on patients (81). Although CAR-T and BCMA-targeted T-cell activators are not recommended as a first- and second-line therapy, early remission needs to be achieved in MM treatment to improve PFS and OS. From an individual perspective, tumor cells have the ability to exist in the body for a long period of time and even the current MRD test can not say for sure that there are no tumor cells in a patient with CR. Further expansion of CAR-T therapy and other immunotherapies can be used as a supplement and assistance to the immune system to fight tumors. The current means should be improved to achieve a longer PFS time for patients, ulimately improving the quality of life. Furthermore, there is still a need to explore the impact on the tumor microenvironment, the process of the emergence of antigen escape and how tumor cells repair damaged DNA when treating with BCMA-targeted CAR-T or bispecific antibody T-cell activators.

Recent studies have shed light on immune-related factors influencing the efficacy of CAR-T cell therapies, particularly in R/R MM. One study on R/R MM demonstrated that patients with higher numbers of activated/functional T cells and fewer CD163+ macrophages prior to treatment were more likely to experience a durable response to CD19 CAR-T-cell therapy (101). Similarly, resistance to BCMA-targeted CAR-T-cell and BCMA-CD3 BiTE therapies in patients with MM has been linked to a distinct immunological profile. Single-cell sequencing of patient samples revealed an increased proportion of terminally exhausted T cells and a low CD4 ratio, and diminished populations of stem cell memory T cells and central memory T cells are associated with CAR-T therapy resistance (102). In addition, upregulation of T cell immunoreceptor with Lg and ITIM domains + NK cells and an increase in interferon-responsive dendritic cells were identified as contributing factors to therapy resistance (103,104). These immune changes are thought to impair the anti-tumor efficacy of CAR-T-cell therapies in MM by promoting T-cell exhaustion and diminishing the overall immune response (105).

In summary, general therapies targeting BCMA, such as CAR-T cells, BiTEs and ADCs, have demonstrated significant efficacy for MM and R/R MM treatment. While CAR-T therapy displays significant therapeutic potential and durability, high cost and accessibility remain major challenges, alongside the complexity of managing resistance mechanisms. Future research should focus on optimizing these therapies to improve patient access, reduce costs and develop strategies to counteract tumor immune evasion, including understanding the tumor microenvironment and resistance pathways. Expanding on these areas may enhance treatment options, potentially extending PFS and OS for patients with MM and R/R MM.

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Availability of data and materials

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Authors' contributions

RX, MW, LW and HZ contributed to the conception of the study. RX, MW, LW, MP, YW and HZ contributed to the drafting of the manuscript; RX, MW, MP, LW and HZ critically revised the manuscript for important intellectual content. Data authentication is not applicable. All authors read and approved the final version of the manuscript and take responsibility for the decision to submit for publication.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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