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Review

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Relapse mechanisms and disease management strategies after BCMA CAR-T therapy for multiple myeloma

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Abstract: Chimeric antigen receptor T-cell (CAR-T) therapy targeting the B-cell maturation antigen (BCMA) has revolutionized the management of relapsed/refractory multiple myeloma (RRMM) by achieving unprecedented initial response rates. Despite this promising outlook, disease relapse remains a critical barrier to long-term remission, underscoring the urgent need to identify resistance mechanisms and optimize therapeutic strategies. This review synthesizes current evidence on the multifactorial drivers of relapse post-BCMA CAR-T therapy, including antigen escape via BCMA loss or trogocytosis, diminished CAR-T cell persistence, immunosuppressive tumor microenvironment remodeling, and T-cell exhaustion. Furthermore, it critically evaluates innovative approaches to overcome relapse, involving next-generation multi-antigen CAR-T constructs, γ-secretase inhibitors to augment BCMA expression, allogeneic CAR-T platforms, and synergistic combinations with immune checkpoint blockade or tumor microenvironment-modulating agents. By integrating preclinical insights with clinical trial data, this work highlights the emerging strategies to enhance CAR-T durability and provides a roadmap for the advancement of therapeutic outcomes in MM. Future directions include biomarker-driven personalization, earlier intervention in treatment sequencing, and combinatorial regimens to holistically address resistance mechanisms. The insights provided by this paper aim to guide translational research and clinical practice, ultimately improving the survival of patients with RRMM.

Key words: Multiple myeloma; BCMA CAR-T therapy; Relapse mechanisms; Antigen escape; Tumor microenvironment; T cell exhaustion

1 Introduction

Multiple myeloma (MM), as a clonal plasma cell malignancy, continues to impose substantial clinical burdens despite recent therapeutic advancements. Over the past two decades, the integration of proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), monoclonal antibodies (e.g., anti-CD38 agents), and autologous stem cell transplantation (ASCT) has significantly improved the overall survival and quality of life of affected patients (Wang et al., 2022b; Dhakal et al., 2021). However, the dynamic clonal evolution of MM cells frequently drives relapse and refractory disease, often mediated by epigenetic plasticity, drug efflux mechanisms, and microenvironmental adaptations (Parikh and Lonial, 2023). These challenges underscore the urgent need for therapeutic options capable of circumventing resistance and achieving sustained disease control.

Chimeric antigen receptor T-cell (CAR-T) therapy represents a paradigm shift in the management of

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hematologic malignancies. Specifically, targeting the B-cell maturation antigen (BCMA), a transmembrane protein highly expressed on malignant plasma cells, has shown remarkable clinical efficacy in relapsed/refractory MM (RRMM). Early-phase trials have reported overall response rates (ORR) exceeding 90%, with durable remissions observed in certain subsets of patients (van de Donk et al., 2021). For instance, the KarMMa trial demonstrated a 73% ORR with idecabtagene vicleucel, while cilta-cel achieved 98% ORR in the CARTITUDE-1 study (Ho et al., 2024). Despite these breakthroughs, relapse remains a critical limitation, with over 50% of patients progressing to disease within 12 months (Wang et al., 2022b). Emerging evidence implicates multifactorial mechanisms—including antigen escape, CAR-T cell dysfunction, and immunosuppressive niche remodeling—as key drivers of therapeutic resistance.

Existing research efforts aim to dissect the above relapse mechanisms and develop counterstrategies. Genomic studies have identified BCMA loss via TNFRSF17 deletions as a major evasion pathway, while functional analyses point to T-cell exhaustion phenotypes and myeloid-derived suppressor cell (MDSC) infiltration as microenvironmental barriers (Samur et al., 2021; Tang et al., 2021; Giannotta et al., 2022). Nevertheless, a systematic synthesis of these findings, particularly in the context of evolving clinical strategies, remains lacking. Thus, this review comprehensively evaluates the biological basis of relapse following BCMA CAR-T therapy, encompassing tumor-intrinsic adaptations, CAR-T product limitations, and microenvironmental crosstalk. Meanwhile, a critical analysis of emerging approaches—such as dual-target CAR designs, γ-secretase modulation, and combinatorial checkpoint inhibition—is provided, that may enhance therapeutic durability (Khan et al., 2022; Cowan et al., 2023; Su et al., 2024). By bridging preclinical insights with clinical trial data, this paper seeks to inform rational therapeutic designs and emphasize future research directions in MM immunotherapy.

2 Current Status of BCMA CAR-T Cell Therapy for Multiple Myeloma

Several BCMA-targeted CAR-T products have been approved for clinical use in MM treatment. Among them, idecabtagene vicleucel (ide-cel) was the first such therapy to receive global regulatory approval. In the pivotal Phase II KarMMa trial, ide-cel demonstrated an ORR of 73% in 128 relapsed/refractory MM (RRMM) patients, with 33% achieving CR and 26% showing a minimal residual disease (MRD)-negative state. Nevertheless, a significant number of patients experienced relapse, with median progression-free survival (PFS) and overall survival (OS) of 8.8 months and 19.4 months, respectively (Sellner et al., 2020). Real-world data have shown similar results, with ORR, CR, PFS, and OS rates of 84%, 42%, 8.5, and 12.5 months, respectively (Ferreri et al., 2023). Another product launched in 2022, cilta-cel, demonstrated an impressive ORR of 98% in the CARTITUDE-1 study, with 82.5% of patients achieving stringent complete remission (sCR); the 27-month PFS and OS rates for cilta-cel were 55% and 70%, respectively (Jagannath et al., 2024). Furthermore, Iqiolelense injection, the first fully human BCMA CAR-T product developed in China, showed an ORR of 96%, an sCR/CR rate of 73%, and a MRD-negative rate of 95%, with a 12-month PFS rate of 78.8%. Table 1 summarizes the key efficacy and relapse/progression data for several BCMA CAR-T trials. These data underscore that despite the promising initial responses, a considerable proportion of patients will eventually experience relapse or disease progression. Therefore, it is essential to develop targeted salvage therapies based on the underlying relapse mechanisms. This review discusses the different relapse mechanisms observed after BCMA CAR-T treatment for MM and proposes potential strategies to improve the survival outcomes for relapsed/refractory MM patients.

Table 1 Clinical trials of BCMA CAR-T cell therapy in MM

Identifer	Vector/co-stimulatory domain	antigen	Phase	No of MM patients	Efficacy			
					ORR(%)	≥CR(%)	PFS(month)	MRD-(%)
NCT04537442	Lentivirus/4-1BB、OX40	BCMA	I	22	100	64	12	71.4
ChiCTR1800018137	Lentivirus/4-1BB	BCMA	I	18	100	72.2	NA	94.4
NCT04181827	Lentivirus/4-1BB	BCMA	III	208	84.6	73.1	NA	60.6
NCT03548207	Lentivirus/4-1BB	BCMA	1b/II	8	100	25	NA	100
NCT03361748	Lentivirus/4-1BB	BCMA	II	128	73	32.8	8.8	25.8
NCT03815383, NCT03751293, NCT04295018, NCT04322292 .	Lentivirus（C-CAR088）/4-1BB	BCMA	I	31	96.4	46.4	NA	48.4
NCT04093596	Lentivirus/4-1BB	BCMA	I	43	55.8	25	NA	93
NCT02658929	Lentivirus/4-1BB	BCMA	I	62	75.8	38.7	8.8	58.3
NCT04155749	Lentivirus/4-1BB	BCMA	I	12	100	75	NA	89
NCT03093168	Retrovirus/4-1BB	BCMA	I-II	49	77	47	10	42.9
NCT04720313	Retrovirus/4-1BB	BCMA	I	20	75	50	5.3	30
NCT03502577	Lentivirus/4-1BB	BCMA	I	18	89	44	11	NA

Abbreviations: MM, multiple myeloma; ORR, overall response rate; CR, complete response; PFS, progression-free Survival; MRD, minimal residual disease.

3 Relapse Mechanisms After BCMA CAR-T Treatment for MM

While multiple myeloma (MM) patients often experience significant clinical remission following BCMA CAR-T therapy, the durability of this response remains suboptimal. More than 50% of patients relapse within 12 months, with the majority exhibiting antigen-positive relapses, suggesting that the immune surveillance capabilities of CAR-T cells cannot be sustained in the long term (Hamadeh et al., 2024). Myeloma immune escape, CAR-T cell dysfunction, and the tumor microenvironment (TME) all contribute to the relapse risk (Figure 1).

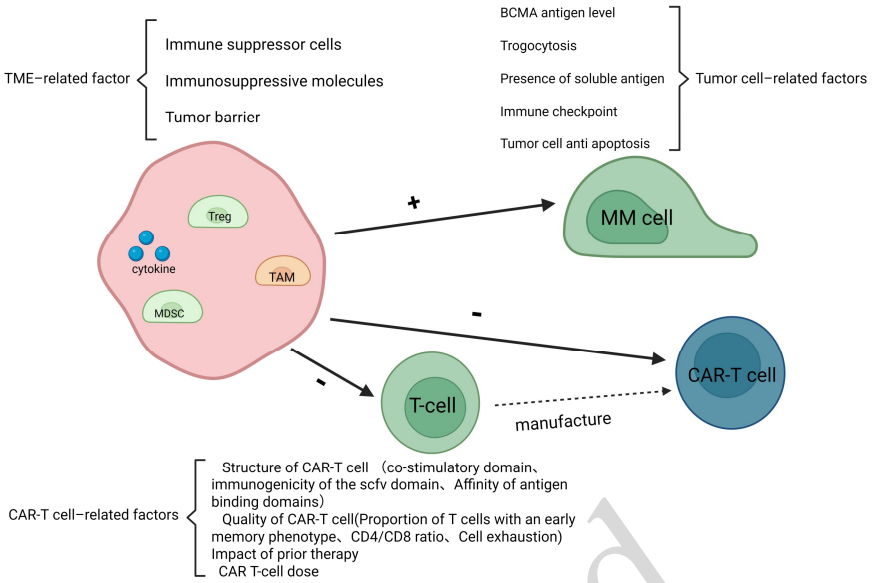

Figure 1 Different relapse mechanisms after BCMA CAR-T treatment. (1) Tumor cell-related factors: various factors cause antigen escape and tumor cell resistance. (2) CAR-T cell-related factors: changes in the structure and properties of CAR-T cells. (3) TME-related factors: immunosuppressive factors such as immunosuppressive cells, immunosuppressive factors and checkpoint molecules in TME. MM, multiple myeloma; Treg, regulatory T cell; TAM, tumor-associated macrophage; MDSC, myeloid-derived suppressor cell.

3.1 Factors Related to Multiple Myeloma Cells

3.1.1 Antigen-Negative Relapse

Multiple myeloma is a highly heterogeneous malignancy, with different subclones expressing varying levels of BCMA on their surface. Several studies have indicated that baseline BCMA expression on tumor cells before treatment can impact the efficacy and persistence of CAR-T cells post-infusion. Specifically, low levels of BCMA can hinder the recognition and binding of CAR-T cells to the target, thereby weakening activation signals that drive CAR-T cell proliferation and differentiation (van de Donk et al., 2021). As a result, CAR-T cells may fail to sustain long-term activity and eventually disappear, leading to immune escape by tumor cells.

Samur et al. performed a genomic characterization of patients who relapsed after the first CAR-T treatment and failed to respond to re-treatment. They identified biallelic BCMA deletions at the TNFRSF17 locus in relapsed MM cells, which exhibited low BCMA expression. This suggested that genetic alterations in MM cells lead to the emergence of subclones with reduced BCMA expression, which may evade CAR-T cell targeting. The selective pressure exerted by treatment likely eliminates MM cell clones with high BCMA expression, allowing BCMA-negative clones to persist and resulting in a decline in surface BCMA levels, thus reducing CAR-T cell activation (Samur et al., 2021).

Trogocytosis, a contact-dependent intercellular material transfer process, has also been implicated in antigen-negative relapse. MM cells can transfer BCMA antigens to CAR-T cells via trogocytosis, causing the mutual destruction of CAR-T cells and facilitating immune escape. This process not only depletes CAR-T cell numbers but also leads to functional exhaustion, further contributing to relapse (Zhai et al., 2023; Hamieh et al., 2019).

The γ-secretase complex in MM patients' bodies can cleave BCMA from the surface of MM cells, significantly reducing BCMA density and limiting CAR-T cell activation. This cleavage also increases the level of soluble BCMA (sBCMA) in peripheral blood, interfering with CAR-T cell recognition of the target antigen, acting as another key factor driving antigen-negative relapse (Chen et al., 2022). Margot et al. demonstrated that

γ-secretase inhibitors (GSIs) can dose-dependently increase BCMA expression on tumor cells and decrease sBCMA in the bone marrow, thereby improving CAR-T cell recognition and tumor targeting (J., 2019). These findings suggest that GSIs may play a crucial role in preventing relapse in MM patients.

3.1.2 Antigen-Positive Relapse Tumor Cell Resistance to CAR-T Cell Killing

CAR-T cells eliminate target cells via the exocytosis of cytotoxic mediators such as granzyme, perforin and tumor necrosis factor. Serine protease inhibitors, which antagonize serine proteases and inactivate granzyme B, have been shown to contribute to tumor cell resistance to CAR-T killing, thereby promoting relapse (Zhang et al., 2024). Furthermore, MM cells can evade CAR-T cell-mediated apoptosis by upregulating anti-apoptotic proteins or downregulating pro-apoptotic proteins (Karlsson, 2016). Members of the c-FLIP family of proteins, which includes several subtypes, compete with caspase-8 for binding to the Fas-associated protein with a death domain (FADD) in the death-inducing signaling complex (DISC), thus blocking caspase-8 activation and resisting apoptosis induced by death receptors (Ergun et al., 2024).

3.2 Factors Related to CAR-T Cells

3.2.1 Baseline State of CAR-T Cells

The quality of CAR-T cell products is influenced by the baseline state of T cells before manufacturing. T cells are collected via apheresis, whereas various factors, such as prior treatments, underlying conditions and genetic variations, can lead to significant differences in baseline T cell subsets, in turn affecting treatment outcomes. In a Phase I clinical trial, Adam et al. treated relapsed/refractory MM patients with a BCMA CAR-T product containing a novel fully human scFv and found that treatment responses were associated with a high CD4/CD8 T cell ratio, a high frequency of CD45RO− CD27+ CD8+ T cells before manufacturing, and greater in vitro expansion during the CAR-T cell production process (Cohen et al., 2019). These findings have been corroborated in other BCMA CAR-T studies, suggesting that naïve T cells (CD45RA+CCR7+CD62L+), early memory T cells (CD45RA+CCR7−CD62L+) and central memory T cells (CD45RA−CCR7+CD62L+) are crucial for robust CAR-T cell expansion and persistence. Products enriched with these T cell subsets demonstrated enhanced proliferation and survival, and lower relapse rates (McLellan and Ali Hosseini Rad, 2019). Furthermore, Arcangeli et al. preselected memory stem cell (TN/SCM) T cells for CAR-T production and demonstrated superior in vivo adaptability, faster expansion and reduced cytokine release syndrome (CRS) in a humanized mouse model (Arcangeli et al., 2022). These results highlight that the inclusion of dysfunctional T cells during early screening may lead to diminished efficacy and toxicity in subsequent treatments.

The pretreatment regimen is a critical factor influencing the baseline T cell state. Heider et al. examined the impact of bortezomib on T cell subsets and found that bortezomib transiently reduced CD4+ lymphocyte counts, causing a temporary immunodeficiency (Heider et al., 2010). Similarly, lenalidomide treatment has been shown to induce a senescent/exhausted phenotype in T cells (Chung et al., 2016). Given that both the frequency of early memory T cells and the CD4/CD8 T cell ratio significantly influence CAR-T cell quality, monitoring T cell dysfunction induced by ongoing anti-MM therapies is essential to avoid suboptimal CAR-T responses.

3.2.2 CAR-T Cell Preparation

The quality of CAR-T cell products is further affected by the preparation process, including the isolation of peripheral blood mononuclear cells (PBMCs) through apheresis. Variability in autologous cells leads to subsequent differences in the composition of PBMCs, which can impact T cell expansion and the overall quality of CAR-T products (Stroncek et al., 2016). Elavia et al. found that an excessive proportion of monocytes in PBMCs reduces CD3+ T cell expansion and increases the CD4/CD8 ratio, while a higher number of neutrophils is inversely correlated with the CD4/CD8 ratio (Elavia et al., 2019). These findings suggest that optimizing PBMC composition by depleting monocytes and granulocytes may improve CAR-T product quality.

Exogenous cytokines also play a pivotal role in CAR-T cell function. Although IL-2 promotes CAR-T cell expansion, it can reduce anti-tumor persistence and increase the proportion of Tregs. In contrast, IL-15 and

IL-17 promote CAR-T cell proliferation while reducing T cell exhaustion and enhancing cytotoxic activity (Sierro-Martinez et al., 2025). TGF-β helps maintain the memory phenotype, and combining IL-21 with IL-2/IL-15 can further enrich the proportion of less differentiated/memory T cells, thereby enhancing CAR-T cell activity (Du et al., 2021).

While shortening the *in vitro* culture period can enhance CAR-T cell expansion and killing ability (Watanabe et al., 2022), it is also important to monitor for potential adverse effects, such as increased expression of checkpoint molecules, which could lead to poorer prognosis.

3.2.3 CAR-T Cell Structure

The co-stimulatory signal domains within the CAR structure, such as CD28 and 4-1BB, play a crucial role in determining the functional characteristics of CAR-T cells. Preclinical studies have shown that CD28 enhances cytokine secretion, cell expansion and tumor-killing activity, while the 4-1BB domain is associated with prolonged persistence and a higher proportion of central memory T cells (TCM) (Cappell and Kochenderfer, 2021). In an engineered CD38 CAR-T trial for anti-MM treatment, researchers compared CAR constructs containing either the CD28 or the 4-1BB signal domain. The results indicated that the CD28 domain lowered the affinity threshold required for cytotoxicity, while the 4-1BB domain reduced inhibitory receptor expression and delayed T cell exhaustion (Drent et al., 2019). According to Salter et al., the performance differences between these two co-stimulatory domains arise from variations in intracellular signaling intensity. The selection of CAR-T products with different co-stimulatory domains may therefore influence the relapse risk. Some studies have also suggested that combining both CD28 and 4-1BB domains can enhance the anti-tumor activity and proliferative capacity of low-affinity CAR-T cells (Pei et al., 2023).

The non-humanized domains, such as single-chain variable fragments (scFv) on CAR-T cell surfaces, may induce host immune responses, leading to the production of anti-CAR antibodies, which in turn can impair CAR-T cell persistence (Khan et al., 2022). Xu et al. developed a CAR-T therapy targeting two distinct BCMA epitopes. Although the treatment achieved a nearly 80% complete remission (CR) rate, anti-CAR antibodies were frequently detected in relapsed patients, resulting in a reduction in CAR-T cell numbers. Optimization strategies to address this issue include pretreatment regimens to deplete lymphocytes and the use of humanized CAR constructs (Xu et al., 2019).

The CAR design also significantly impacts CAR-T cell exhaustion. Webster et al. engineered an AP1-NFκB promoter to attenuate CAR expression in the absence of antigenic stimulation, effectively reducing tonic signaling and alleviating T cell exhaustion (Stavrou et al., 2018). Similarly, Michael et al. explored different extracellular spacer lengths in CD19 CARs expressed in CD8+ CAR-T cells. They found that CAR-T cells with shorter spacers exhibited higher cytokine secretion and more effective signal transduction upon antigen recognition. In vivo experiments confirmed that these T cells had enhanced tumor elimination capabilities and superior persistence (Hudecek et al., 2015). Furthermore, some studies have shown that CAR-T cells using the IgG2 Fc sequence, with lower FcγR binding affinity, exhibited weaker tonic signaling compared to those using the IgG1 CH2 sequence, further emphasizing the importance of spacer composition in CAR-T cell exhaustion.

3.3 Factors Related to the Multiple Myeloma Microenvironment

The tumor microenvironment, which refers to the complex milieu surrounding myeloma cells, including the extracellular matrix, cytokines, blood and lymphatic systems, immune cells, and endothelial cells, supports tumor cell proliferation, growth and invasion. The TME is replete with immunosuppressive factors that can hinder the activity of CAR-T cells, contributing to relapse following treatment (Garcia-Ortiz et al., 2021).

3.3.1 Immunosuppressive Cells

A variety of immunosuppressive cells are present in the TME, which significantly disrupt the local anti-tumor activity and persistence of CAR-T cells. Myeloid-derived suppressor cells (MDSCs) are a

heterogeneous population derived from immature bone marrow cells. Research has shown that MDSCs can be activated by the uptake of exosomes from MM tumor cells, and they secrete inhibitory factors, including nitric oxide (NO), reactive oxygen species (ROS), IL-10, and TGF-β. MDSCs also consume key amino acids, such as arginine and cysteine, and promote the differentiation and maturation of regulatory T cells (Tregs). These actions inhibit T cell expansion, induce MM progression and promote angiogenesis (Giannotta et al., 2022). Fultang et al. demonstrated that targeting MDSCs with the anti-CD33 monoclonal antibody gemtuzumab enhanced the anti-tumor activity of CAR-T cells, suggesting that a high level of MDSCs may inhibit CAR-T cell efficacy (Fultang et al., 2019). Recent studies have also highlighted the role of the highly expressed V-domain Ig suppressor of T cell activation (VISTA) in MDSCs as a key negative regulator of T cell function within the TME (Wang et al., 2018).

The presence of regulatory T cells (Tregs) in the bone marrow is also linked to poor prognosis in MM patients. Tregs inhibit T cell function via activation of the CD39/CD73 adenosine pathway and contribute to tumor angiogenesis through their secretion of TGF-β, which triggers the VEGF pathway in tumor cells (Ding and Wu, 2024). These mechanisms of immunosuppression are significant contributors to relapse after CAR-T treatment.

Tumor-associated macrophages (TAMs) exhibit considerable plasticity and heterogeneity, with a particularly notable example being M2-type TAMs expressing the folate receptor (FRβ). These M2-type TAMs secrete immunosuppressive factors, including TGF-β1, IL-10, arginase-1, as well as angiogenic factors like VEGF and FGF-2, which promote tumor growth and inhibit CAR-T cell activity, further facilitating relapse (Wang et al., 2022a).

3.3.2 Immune Checkpoint Molecules

Immune checkpoint molecules are key immunosuppressive factors within the TME. During the progression of multiple myeloma (MM), tumor cells promote the decline or dysfunction of T cell activity by upregulating the expression of these molecules, leading to drug resistance and relapse. For instance, the PD-L1 ligand is widely expressed on both hematopoietic and non-hematopoietic cells. Upon binding to PD-1, PD-L1 inhibits the PI3K/protein kinase B (Akt) and RAS/MEK/ERK signaling pathways in T cells, thereby blocking protein kinase C-theta function, glycolysis, and phosphatidylinositol signaling through ZAP70. This significantly suppresses the anti-tumor immune function of T cells (Garcia-Ortiz et al., 2021). The combination of CAR-T cell therapy and immune checkpoint inhibitors (ICIs) not only enriches tumor-killing cells within the TME, thereby enhancing the efficacy of ICIs, but also reduces the inhibitory effects of tumor cells on CAR-T cells, making this combination a promising approach (Su et al., 2024; Zhou et al., 2024). It has garnered considerable attention as a potential strategy to overcome immune resistance in MM treatment (Figure 2).

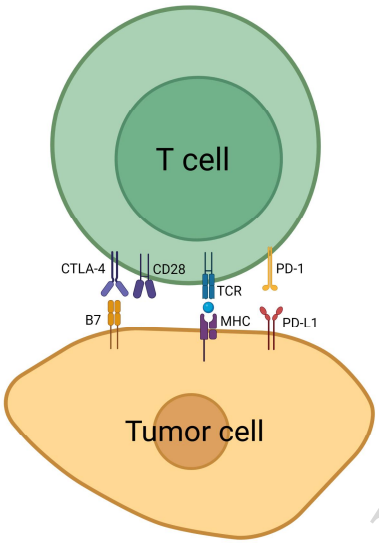

Figure 2 Mechanism of action of immune checkpoints. (1) PD-1 is expressed on the surface of T cells. When it binds to PD-L1 on the surface of tumor cells, it transmits inhibitory signals to T cells, inhibiting T cell proliferation, cytokine secretion, and cytotoxicity. (2) CTLA-4 is mainly expressed on the surface of activated T cells, competing with the co-stimulatory molecule CD28 on their surface for binding to the B7 molecule (CD80/CD86) on the surface of tumor cells, thereby inhibiting the initial activation of T cells. (3) When endogenous TCR (CAR-T cells still retain their own TCR) binds to MHC-antigen peptides, it triggers the T cell activation pathway and induces the expression of immune checkpoint molecules (such as PD-1, CTLA-4). PD-1, programmed cell death protein 1; PD-L1, programmed death ligand-1; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; TCR, T cell receptor; CAR-T, chimeric antigen receptor T cell; MHC, major histocompatibility complex.

3.3.3 Microenvironment of Extramedullary Disease (EMD)

Approximately 40% of multiple myeloma patients develop extramedullary disease (EMD). Qi et al. analyzed 31 relapsed/refractory MM (RRMM) patients with bone EMD who were treated with combined BCMA and CD19 CAR-T therapy. The results revealed that, in contrast to medullary disease, the response to treatment in EMD patients was poor, with most showing either progressive disease (PD) or stable disease (SD). The time to the first and best response was delayed and the duration of response was shorter. Additionally, the overall survival of EMD patients following treatment was significantly worse than that of non-EMD patients (Qi et al., 2023). These findings suggest that the presence of EMD in MM patients represents a major adverse factor limiting the efficacy of CAR-T therapy.

Maria et al. highlighted that the complex microenvironment in EMD is characterized by hypoxia, nutrient deprivation, high levels of inhibitory cytokines, and an acidic pH. The expression of extravasation regulatory factors, such as L-selectin, Mac-1, TNF-α, and ICAM-1, is downregulated in the blood vessels, leading to disorganized vascular structures that create a physical barrier impeding the infiltration, proliferation, and survival of CAR-T cells. Furthermore, as EMD progresses, tumor gene heterogeneity increases and clonal plasma cells accumulate in later stages of the disease, which further impairs the recognition and targeting by CAR-T cells, thus explaining the poor treatment outcomes in EMD patients.

Recent studies have emphasized that, similar to the bone marrow TME, EMD is also characterized by the accumulation of immunosuppressive cells, including myeloid-derived suppressor cells (MDSCs) and T cells exhibiting an exhausted phenotype. This creates a highly immunosuppressive environment that hinders the survival and function of CAR-T cells (Dhodapkar et al., 2022; Graham and Maus, 2022; Yao et al., 2023). For patients with EMD, further studies are required to investigate the specific characteristics of the TME in both bone marrow and EMD sites, as well as the kinetics of CAR-T cell treatment. Paired biopsies would be essential for elucidating the mechanisms of resistance and optimizing treatment strategies.

4 Coping Strategies

The efficacy of BCMA CAR-T therapy in relapsed/refractory multiple myeloma (RRMM) patients is often limited by several factors, including tumor cell antigen escape, poor T cell persistence, and an inhibitory TME (Yue et al., 2025). To overcome these challenges, many innovative approaches have been explored in clinical studies, with the aim to reduce relapse risk and provide more durable remissions and improved quality of life for RRMM patients (Table 2).

Table 2 Strategies targeting the recurrence mechanisms of BCMA CAR-T

Resistance Mechanism		Strategies	Clinical Trial
MM cell factor	Negative recurrence Positive recurrence	New/Dual-/Multi-target CAR-T/Cocktail therapy	ChiCTR2100048888 NCT04674813 ChiCTR1800018143
		Gamma-secretase inhibitors	NCT03502577
		Resistance to Trogocytosis	NA
T-cell factor	CAR-T cell production	Increase the proportion of memory cells	NCT04093596
		Reduce CAR immunogenicity	ChiCTR1800018137
	T cell exhaustion Previous treatment plan	Next generations of CAR-T cells	NCT03778346
TME factor	Immunosuppressive cells Immune checkpoint molecules EMD microenvironment	Immune checkpoint inhibitors	NCT05191472
		Combined ASCT	NCT03455972
		Combined with other drugs	NA

Abbreviations: TME, tumor microenvironment; EMD, extramedullary disease; ASCT, autologous stem cell transplantation.

4.1 Overcoming Multiple Myeloma Cell-Related Factors

4.1.1 New Target CAR-T

BCMA antigen escape is a major factor affecting the intensity and persistence of CAR-T cell responses, contributing to relapse (Rana et al., 2022). To avoid antigen-negative relapse, many studies are focusing on developing CAR-T cells targeting alternative antigens, such as CD19, CD138, CD38, GPRC5D, SLAMF7, NKG2D, CD56, κ light chain, CD229, TACI, among others (Figure 3, Table 3).

G protein-coupled receptor class C group 5 member D (GPRC5D) is a promising target, as it is highly expressed in MM cells but restricted to the skin and hair follicles in normal tissues. In a Phase II trial, anti-GPRC5D CAR-T treatment achieved an overall response rate (ORR) of 91% in 33 RRMM patients involving 9 patients who had previously undergone BCMA CAR-T therapy. Among them, 79% achieved minimal residual disease (MRD) negativity (Xia et al., 2023). In a Phase I trial, 71% of patients responded to MCARH109 (a GPRC5D CAR-T product), with the high-dose group showing a better response rate (Mailankody et al., 2022). These results suggest that CAR-T targeting GPRC5D has a strong induction response, particularly in patients who have failed or progressed after BCMA CAR-T therapy. Nonetheless, dose-dependent efficacy differences highlight the importance of optimizing dosing strategies.

SLAMF7, another target highly expressed in MM cells, has shown promising preclinical results (Prommersberger et al., 2021). Meanwhile, the autophagy induced in normal cells by SLAMF7 expression needs to be addressed before clinical application (Gogishvili et al., 2017). The main focus of current research on new target CAR-T therapies is to identify antigens that are stably expressed on MM cells, have minimal expression in normal tissues, exhibit low auto-heterogeneity, and are not highly soluble (Timmers et al., 2019).

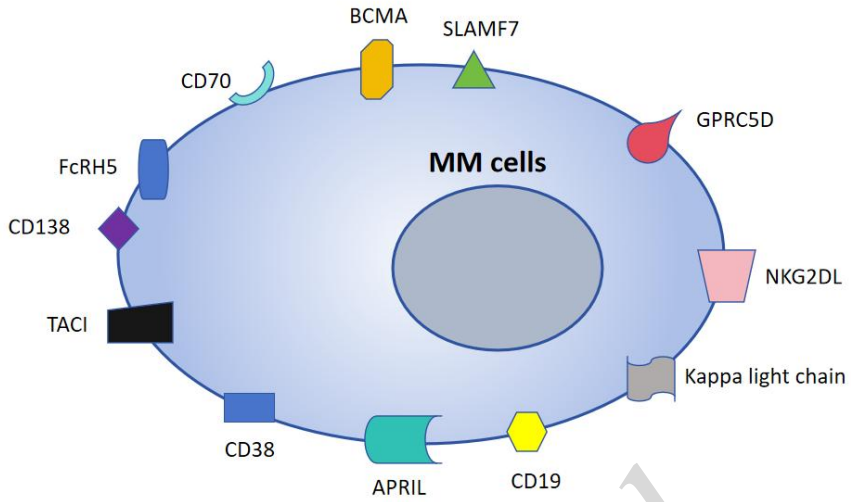

Figure 3 Potential target found on MM and being investigated in clinical trials. BCMA, B-cell maturation antigen; SLAMF7, signaling lymphocyte activation molecule family member 7; GPRC5D, G protein-coupled receptor class C group 5 member D; NKG2DL, natural killer group 2 member D ligands; APRIL, A proliferation-inducing ligand; TACI, transmembrane activator and CAML interactor; FcRH5, Fc receptor homolog 5; CD, cluster of differentiation.

Table 3 Non-BCMA-targeted CAR-T clinical trials for MM

Neoantigen	Vector/co-stimulatory domain	Identifer(Status)	Phase	No of MM patients	Efficacy			
					ORR(%)	≥CR(%)	PFS(month)	MRD-(%)
CD19	Lentivirus/4-1BB	NCT02135406(completed)	I	10	80	NA	NA	NA
GPRC5D	Lentivirus/NA	NCT04674813(active)	I	17	94	71	NA	67
SLAMF7	Sleeping beauty transposon/NA	EudraCT2019-001264-30(active)	I-II	38	NA	NA	NA	NA
CD138	Lentivirus/4-1BB	NCT01886976(NA)	I-II	5	80	NA	3	NA
NKG2DL	γ-retrovirus/Dap10 signaling	NCT02203825(completed)	I	5	NA	NA	NA	NA
CD38	Lentivirus/NA	NCT03464916(active)	I	72	NA	NA	NA	NA
CD70	Lentivirus/4-1BB	NCT04662294(recruiting)	I	108	NA	NA	NA	NA

Abbreviations: MM, multiple myeloma; ORR, overall response rate; CR, complete response; PFS, progression-free Survival; MRD, minimal residual disease.

4.1.2 Multi-target CAR-T

To combat relapses caused by low BCMA levels, multi-target CAR-T cells have emerged as an effective strategy. These include CAR-T cells expressing multiple CARs or a single CAR structure with multiple tandem single-chain variable fragment (scFv) domains. Research has shown that multi-target CAR-T approaches may offer greater potential than traditional cocktail therapies (Table 3). This enhanced efficacy may stem from the formation of bivalent immunological synapses that increase intercellular affinity and reduce competitive inhibition.

In a Phase I clinical trial, the BCMA/CD38 bispecific BM38 CAR developed by Heng et al. demonstrated an overall remission rate (CR) of 87% and a stringent complete remission rate (sCR) of 52% in 23 RRMM

patients. The one-year overall survival (OS) rate was 93%, with manageable toxicity (Mei et al., 2021). BCMA/CD19, BCMA/GPRC5D, and BCMA/TACI tandem CAR constructs have also shown promising remission rates in preclinical studies (Tang et al., 2020; Fernandez de Larrea et al., 2020).

When developing multi-target CAR-T cells, it is crucial to optimize the design of scFvs, spacer sequences, and linkers to ensure the compactness and functionality of the CAR structure. Studies have indicated that systematic optimization can significantly improve the activity of bispecific CAR-Ts (Zah et al., 2020). Furthermore, combining multi-antigen CAR-T with other anti-tumor therapies may create a synergistic effect, which warrants further exploration (Lin et al., 2019).

Table 4 Multi-target CAR-T clinical trials for MM

Dual-targeted	Identifer	Phase	No of MM patients	Efficacy			
				ORR(%)	≥CR(%)	PFS(month)	MRD-(%)
2 distinct BCMA epitopes	NCT02135406(completed)	I	10	80	NA	NA	NA
BCMA/GPRC5D bispecific CAR-T cells	NCT04674813(active)	I	17	94	71	NA	67
BCMA/CD19 bispecific CAR-T cells	EudraCT2019-001264-30(active)	I-II	38	NA	NA	NA	NA
BCMA/CD19 bispecific CAR-T cells	NCT01886976(NA)	I-II	5	80	NA	3	NA
BCMA/CD38 bispecific CAR-T cells	NCT02203825(completed)	I	5	NA	NA	NA	NA
Combined infusion of anti-BCMA and anti-CD19 CAR-T cells	NCT04662294(recruiting)	I	108	NA	NA	NA	NA

Abbreviations: MM, multiple myeloma; ORR, overall response rate; CR, complete response; PFS, progression-free Survival; MRD, minimal residual disease.

4.1.3 γ-Secretase Inhibitors

Gamma secretase inhibitors (GSIs) have been shown to upregulate BCMA expression on the surface of MM cells. Pont et al. treated MM cell lines with GSIs and found that after 24 hours, the BCMA concentration on MM cells increased and the soluble BCMA (sBCMA) level decreased significantly. This effect was dose-dependent and enhanced the killing ability of BCMA CAR-T cells (Cowan et al., 2023). Similar results were observed in mouse models.

Cowan and colleagues evaluated the clinical effects of combining BCMA CAR-T with crenigacestat (a GSI) in 18 RRMM patients. The ORR was 89%, with 55% of patients achieving CR or sCR. One patient maintained sCR for over 4 years, and the median progression-free survival (PFS) was 11 months. Importantly, the median BCMA density on MM cells increased by 12.2-fold after GSI treatment (Cowan et al., 2023). These findings suggest that GSIs can effectively prevent antigen escape after CAR-T therapy by upregulating BCMA expression. However, clinicians must be cautious of potential dose-dependent adverse effects, such as neurotoxicity, cytokine release syndrome, and gastrointestinal toxicity (Cowan et al., 2023). Other studies have also indicated that inhibitors like See61 and HDAC7 can increase BCMA expression and work synergistically with GSIs (Ramkumar et al., 2020).

4.1.4 Resisting Trogocytosis

Trogocytosis-mediated immune escape is a well-established mechanism of relapse after CAR-T therapy.

In addition to using new target CAR-T and multi-antigen CAR-T strategies to address antigen loss, some studies on CD19 CAR-T for B-cell malignancies have suggested that improving CAR design can help alleviate trogocytosis (Chen et al., 2024). Olson et al. co-cultured low-affinity CD19 CAR-T cells with tumor cells and found that, compared to high-affinity CAR-T constructs, low-affinity CD19 CAR-T cells significantly increased antigen levels on tumor cell surfaces, showed less apoptosis, maintained higher anti-tumor activity, and demonstrated better persistence in animal models. This was attributed to a significant reduction in trogocytosis by low-affinity CAR-T cells (Olson et al., 2022).

Recent studies have also demonstrated that combining CD19 monoclonal antibodies with CAR-T cells can accelerate the dissociation of CAR-T cells from tumor cells, reducing their interaction and thus minimizing trogocytosis. This combination significantly enhanced tumor killing in both *in vitro* and *in vivo* experiments (Koh et al., 2025). These data suggest that the combination of monoclonal antibodies with CAR-T therapy holds research potential. Future studies should investigate the applicability of this approach to other common MM targets, such as BCMA, and explore its clinical relevance.

4.2 Overcoming CAR-T Cell-Related Factors

4.2.1 Increase in the Proportion of Memory Cells

The efficacy of CAR-T cell therapy is closely linked to the baseline phenotype of T cells. Naïve T cells, stem cell memory T cells and central memory T cells typically exhibit more sustained and robust cytotoxic activity (Kong et al., 2023). However, the significant variation in the composition of T-cell subsets across different patients poses a challenge. To optimize the functionality of CAR-T products, it is essential to emphasize the importance of early T-cell collection from patients and implement strategies to raise the proportion of memory cells.

Research has demonstrated that cytokines such as IL-7, IL-15 and IL-2 can effectively promote the expansion of CD8+ memory T cells and enhance their cytotoxic capabilities. JQ1, an inhibitor of bromodomain and extraterminal (BET) proteins, can preserve the functional characteristics of central memory T cells and improve the in vivo persistence of CAR-T cells by directly modulating BATF expression, thereby reducing their differentiation into effector cells (Kagoya et al., 2016). Similarly, rapamycin has been shown to promote the generation of CD8+ memory T cells through analogous mechanisms (Rao et al., 2010).

In addition to small-molecule drugs, the use of allogeneic universal CAR-T cells derived from healthy donors offers a promising avenue to overcome the limitations imposed by patients' individual immune profiles. Allo-715, an allogeneic BCMA CAR-T product with a genetically engineered disruption of the TCRα constant gene, has shown encouraging results in Phase I trials. Specifically, in the 320 × 106 CAR-T cell dose cohort, the objective response rate (ORR) was 70.8%, with 25% of patients achieving a complete response (CR) or stringent complete response (sCR). The median duration of response (DOR) was 8.3 months, indicating the potential feasibility of allogeneic CAR-T therapy (Mailankody et al., 2023). More recent developments have explored universal CAR-T cells derived from γδ T cells, which are capable of triggering both innate and specific immune responses through natural killer receptors (NTRs) and CARs simultaneously. These cells demonstrate enhanced cytokine secretion and cytotoxicity and are less likely to induce toxic side effects such as graft-versus-host disease (GVHD). However, the safety and efficacy of allogeneic CAR-T cells require further validation in larger clinical trials (Hamadeh et al., 2024; Jain et al., 2020).

4.2.2 Reduction of CAR Immunogenicity

The persistence of murine-derived single-chain variable fragments (scFvs) in CAR-T cells is significantly influenced by immune rejection. Studies have indicated that the use of humanized or fully human scFvs in CAR structures can effectively circumvent host anti-CAR immunity, thereby maintaining the anti-tumor activity of CAR-T cells. In a Phase I clinical trial, a fully human BCMA scFv (CT103A) was used to construct CAR-T cells for patients with BCMA-positive relapsed/refractory multiple myeloma (RRMM). A rapid and high response rate (ORR of 100%, sCR of 72.2%) was achieved, with three out of four patients who had previously

relapsed after receiving murine-derived BCMA CAR-T showing sCR. The incidence of cytokine release syndrome (CRS) was within acceptable limits and no immune effector cell-associated neurotoxicity syndrome (ICANS) was observed, highlighting the safety and efficacy of humanized scFv CAR-T therapies (Wang et al.,2021). Several humanized BCMA CAR-T products, such as FHVH33, ARI0002h, MCARH171, and orva-cel, are currently undergoing clinical evaluation.

Pre-conditioning with chemotherapy drugs like cyclophosphamide, etoposide, or fludarabine has been shown to effectively mitigate CAR immunogenicity by eliminating host lymphocytes (Ramos et al., 2019). Moreover, some studies have suggested that decoupling the scFv structure from the CAR-T construct may help prevent the immune-mediated clearance of CAR-T cells. For instance, the SUPPER CAR, which employs zipper components derived from human transcription factors, not only allows a single CAR to target multiple antigens but also reduces immunogenicity (Denham et al., 2019).

4.2.3 Reduction of CAR-T Cell Exhaustion

T-cell exhaustion, that may be caused by various factors, contributes to the poor persistence and limited therapeutic efficacy of CAR-T cells in RRMM patients. Third-generation CAR-T cells, which incorporate multiple co-stimulatory domains in addition to CD3ζ, have been shown to enhance persistence and maintain cytotoxic activity, thereby reducing early CAR-T cell exhaustion (Rujirachaivej et al., 2024). Fourth-generation CAR-T cells, which can secrete specific cytokines to stimulate innate immune cells for anti-tumor activity, have demonstrated improved efficacy through immunomodulation, helping to prevent the impairment of CAR-T function (Duan et al., 2021). Recent studies have also suggested that epigenetic modifications, such as knocking out the de novo DNA methyltransferase 3α (DNMT3A) gene or using decitabine to block methylation, may help sustain a higher proportion of memory CAR-T cells, providing new perspectives for overcoming apoptosis and enhancing CAR-T efficacy (Ladle et al., 2016).

4.3 Overcoming the Inhibitory Tumor Microenvironment

4.3.1 Combination with Immune Checkpoint Inhibitors

Following infusion, CAR-T cells often experience functional exhaustion due to the increased expression of immune checkpoint molecules on their surfaces, which contributes significantly to immune tolerance within the TME. Therefore, the combination of CAR-T therapy with immune checkpoint inhibitors (ICIs) has emerged as a promising strategy to enhance the anti-tumor effect. The primary immune checkpoints targeted in these strategies include PD-1, PD-L1, CTLA-4, and TIM-3.

Bernabei et al. investigated the combination of CAR-T therapy with pembrolizumab (a PD-1 inhibitor) in five patients who exhibited tumor progression after BCMA CAR-T treatment. The results showed that the addition of pembrolizumab promoted CAR-T cell proliferation and induced partial remission, although the response was transient. Other studies have substantiated the synergistic effects of combination therapies, demonstrating enhanced tumor cell killing, improved CAR-T cell effector function, and prolonged persistence (Bernabei et al., 2018). However, these modalities still have certain limitations, including the potential for adverse immune reactions caused by ICIs and the short half-life of these agents, which complicate long-term therapy (Najafi and Mortezaee, 2024). Furthermore, the timing of ICI administration significantly influences the outcome of combination therapy. Research suggests that introducing ICIs after CAR-T infusion may yield more robust therapeutic effects (Hirayama et al., 2024).

To address the challenges associated with external combination therapies, researchers have been exploring self-modifying CAR-T cells. Genetic engineering techniques can enable CAR-T cells to autonomously produce anti-PD-1 antibodies, thereby overcoming dosing frequency limitations. CRISPR/Cas9 technology has also been employed to edit CAR-T cell genomes to reduce PD-1 expression, and construct CAR-T cells capable of secreting scFv structures that block immunosuppressive checkpoint molecules (Hong et al., 2020). These approaches hold great promise for improving CAR-T cell effector function, promoting cytokine secretion, and enhancing anti-tumor responses.

4.3.2 Combination CAR-T with Autologous Transplantation

The TME can impede the persistence of BCMA CAR-T cells in vivo. However, studies highlighted that combining autologous stem cell transplantation (ASCT) with CAR-T therapy can achieve a synergistic effect. Following ASCT, patients experience lymphocyte depletion and a reduced tumor burden, leading to a favorable immune environment for CAR-T cells to exert their therapeutic effects (Janakiram et al., 2022). Furthermore, CAR-T cell therapy can help clear residual tumor cells post-transplant and improve T-cell function within the TME, consolidating and enhancing the effect of ASCT while reducing relapse risk (Yuan et al., 2024). In a study by Shi et al., patients with RRMM underwent ASCT, followed by CD19 or BCMA CAR-T cell therapy and maintenance with lenalidomide. All patients responded, with an ORR of 100% and 90% achieving sCR. The minimal residual disease (MRD)-negative rate was 50%, with 70% of patients maintaining MRD negativity at a median follow-up of 42 months. The combination of CAR-T and ASCT demonstrated excellent anti-tumor efficacy (Shi et al., 2022). However, the combination of ASCT with CAR-T therapy is not without drawbacks. Ding et al. reported that patients in the non-transplantation group exhibited better ORR, overall survival (OS) and progression-free survival (PFS) compared to those who underwent transplantation. This discrepancy may be due to T-cell dysfunction and exhaustion following ASCT, which could limit the expansion and efficacy of CAR-T cells (Ding et al., 2024). Therefore, future large-scale trials are needed to assess the long-term efficacy and optimal use strategy of combining ASCT with CAR-T therapy.

4.3.3 Other Drug Combination Therapies

The TME contains immunosuppressive components, including bone marrow stromal cells as well as immunosuppressive cells and molecules, all of which contribute to the survival of multiple myeloma (MM) cells and the development of resistance to CAR-T therapy. Many clinical trials are currently investigating combination strategies to counteract the immunosuppressive effects of the TME and restore CAR-T cell function.

Chemotherapy drugs can induce lymphocyte depletion and enhance the endogenous anti-tumor immune response. For instance, low-dose cyclophosphamide pretreatment before CAR-T infusion has been shown to improve the inflammatory characteristics of the TME, promote CAR-T cell infiltration and reduce Treg cells, thereby enhancing CAR-T cell efficacy. Cyclophosphamide also increases the production of cytokines such as IL-2, IL-7 and IL-15, further supporting T-cell proliferation and reducing immunosuppressive factors in the TME (Murad et al., 2021; Xia et al., 2024). In addition to chemotherapy, pre-treatment with low-dose radiotherapy can recruit endogenous immune cells, improve the immunosuppressive TME, and enhance CAR-T cell activity (Liang et al., 2023). While combining chemotherapy and radiotherapy can improve CAR-T therapy, the careful management of drug doses is essential to avoid toxic side effects.

Other anti-MM drugs, including CD38-targeted inhibitors, have shown promise in reshaping the TME by eliminating antigen-positive MM cells, Treg cells and MDSC cells, thereby enhancing CAR-T cell function. Another promising approach involves using oncolytic viruses to generate an inflammatory TME. Oncolytic viruses can enhance the immunogenicity of the TME, promote immune cell infiltration and stimulate an anti-tumor immune response, thereby improving CAR-T cell therapy (Mardi et al., 2022; Harrington et al., 2019; Davola and Mossman, 2019).

5 Conclusions

BCMA-targeted CAR-T cell therapy has revolutionized the treatment landscape for relapsed/refractory multiple myeloma (RRMM) by offering remarkable clinical responses. However, relapse after initial remission remains a major issue, driven by multifactorial mechanisms including antigen loss, immunosuppressive TME, T cell exhaustion, and limited persistence of CAR-T cells.

Understanding the complex relapse mechanisms is critical for the development of next-generation CAR-T

cell therapies and combination strategies. Current approaches such as dual-antigen targeting, armored CAR-T designs and integration with immune checkpoint inhibitors or γ-secretase inhibitors are showing promising results in preclinical and early clinical studies. Moreover, the optimization of CAR-T cell manufacturing processes and patient preconditioning regimens may further enhance therapeutic efficacy and durability.

Looking ahead, integrating CAR-T therapy into earlier lines of treatment, leveraging synergistic drug combinations, and personalizing therapy based on predictive biomarkers may transform the current therapeutic paradigm for multiple myeloma. At the same time, continued research and well-designed clinical trials will be pivotal to overcoming resistance and improving long-term outcomes in this patient population.

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Author contributions

Yongxian HU conceptualized the manuscript. Jiahao HE was involved in conceptualization, investigation, writing-original draft, writing-review and editing, and visualization. He HUANGand Guoqing WEI was involved in writing-review and editing and supervision. All authors contributed to the article and approved the final manuscript.

Compliance with ethics guidelines

Jiahao He, Yongxian Hu, He Huang, and Guoqing Wei declare that they have no conflict of interest. This article does not contain any studies with human or animal subjects performed by any of the authors.

Declaration on the use of generative AI tools

During the preparation of this work the authors used ChatGPT in order to improve language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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