Postprint of a Meta-Analysis of the Efficacy and Safety of Dual-Target Chimeric Antigen Receptor T-Cell Therapy in Patients with Relapsed/Refractory Multiple Myeloma

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Abstract

Background Chimeric antigen receptor (CAR)-T cell immunotherapy has achieved favorable efficacy in multiple myeloma (MM), with B-cell maturation antigen (BCMA) being the most common target. The disadvantage of single-target CAR-T cell immunotherapy is that it can lead to disease resistance and relapse, possibly related to antigen escape. To address this, dual-target CAR-T cells have been developed for the treatment of relapsed/refractory multiple myeloma (RRMM), although systematic clinical analysis in this area is still lacking.

Objective To conduct a meta-analysis of the efficacy and safety of dual-target CAR-T cell immunotherapy in patients with RRMM.

Methods A computerized search was conducted in seven databases including PubMed, Embase, Cochrane Library, Web of Science, CNKI, Wanfang Data Knowledge Service Platform, and VIP for single-group rate studies on dual-target CAR-T cell therapy for RRMM, with the search period from database inception to February 6, 2023. Two researchers used a self-designed data form to extract and collect data, and the Methodological Index for Non-Randomized Studies (MINORS) was employed for literature quality assessment. Data analysis was performed using RStudio software.

Results A total of 9 studies involving 200 RRMM patients who had previously received multiple lines of therapy were included. Dual-target CAR-T cell therapies could be classified into four categories based on different targets: BCMA+CD19, BCMA+CD38, BCMA+TACI, and BCMA+CS1, with BCMA+CD19 being the most frequently studied target. According to different infusion modalities, CAR-T cell therapies could be divided into four

types: bispecific CAR-T cells, combined or sequential infusion of two different CAR-T cells, bicistronic constructs, and co-transduction. Meta-analysis showed that dual-target CAR-T cell therapy for RRMM achieved an overall response rate (ORR) of 90% (95%CI=0.849~0.943), a complete response rate (CRR) of 54.6% (95%CI=0.416~0.673), a minimal residual disease (MRD) negativity rate of 75.6% (95%CI=0.489~0.952), an extramedullary disease (EMD) overall response rate of 55.1% (95%CI=0.234~0.851), a relapse rate at last follow-up of 29.7% (95%CI=0.141~0.454), a survival rate at last follow-up of 75.6% (95%CI=0.554~0.915), a grade 3-4 cytokine release syndrome (CRS) incidence of 16.4% (95%CI=0.094~0.245), and a neurotoxicity (ICANS) incidence of 4% (95%CI=0.040~0.120). Sensitivity analysis indicated stable results. Egger's test showed that ORR (P=0.03) and EMD overall response rate (P=0.02) suggested a certain risk of bias; CRR (P=0.53), MRD negativity rate (P=0.79), relapse rate at last follow-up (P=0.71), survival rate at last follow-up (P=0.98), grade 3-4 CRS incidence (P=0.90), and ICANS incidence (P=0.30) indicated no publication bias.

Conclusion Dual-target CAR-T cell immunotherapy demonstrates favorable efficacy and safety in RRMM, and future multi-center, large-sample studies with longer follow-up periods are needed to further evaluate its efficacy and safety.

Full Text

Efficacy and Safety of Dual-Targeted Chimeric Antigen Receptor-T Cell Therapy in Patients with Refractory-Relapsed Multiple Myeloma: A Meta-Analysis

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Abstract

Background: Chimeric antigen receptor (CAR)-T cell immunotherapy has achieved promising therapeutic outcomes in multiple myeloma (MM), with B-cell maturation antigen (BCMA) being the most common target. However, single-target CAR-T therapy is limited by disease resistance and relapse, likely due to antigen escape. Dual-targeted CAR-T cell therapy has been developed to address this limitation in refractory-relapsed multiple myeloma (RRMM), though systematic clinical analysis remains lacking.

Objective: To conduct a meta-analysis evaluating the efficacy and safety of dual-targeted CAR-T cell immunotherapy in RRMM patients.

Methods: We systematically searched PubMed, Embase, Cochrane Library, Web of Science, CNKI, Wanfang, and VIP databases for single-group rate studies on dual-targeted CAR-T cell therapy in RRMM from inception to February 6, 2023. Two investigators independently extracted data using a customized form and assessed study quality using the Methodological Index for Non-Randomized Studies (MINORS). Data analysis was performed using RStudio software.

Results: Nine studies involving 200 heavily pretreated RRMM patients were included. Dual-targeted CAR-T cell therapies were categorized into four types based on target combinations: BCMA+CD19, BCMA+CD38, BCMA+TACI, and BCMA+CS1, with BCMA+CD19 being the most frequently studied. Based on infusion modalities, they were classified as: bispecific CAR-T cells, combined or sequential infusion of two different CAR-T cells, bicistronic constructs, and cotransduction. Meta-analysis showed an overall response rate (ORR) of 90% (95%CI=0.849–0.943), complete response rate (CRR) of 54.6% (95%CI=0.416–0.673), minimal residual disease (MRD) negativity rate of 75.6% (95%CI=0.489–0.952), extramedullary disease (EMD) overall response rate of 55.1% (95%CI=0.234–0.851), relapse rate at last follow-up of 29.7% (95%CI=0.141–0.454), survival rate at last follow-up of 75.6% (95%CI=0.554–0.915), grade 3–4 cytokine release syndrome (CRS) incidence of 16.4% (95%CI=0.094–0.245), and immune effector cell-associated neurotoxicity syndrome (ICANS) incidence of 4% (95%CI=0.040–0.120). Sensitivity analysis confirmed stable results. Egger's test indicated potential publication bias for ORR (P=0.03) and EMD overall response rate (P=0.02), while no significant bias was found for CRR (P=0.53), MRD negativity rate (P=0.79), relapse rate (P=0.71), survival rate (P=0.98), grade 3–4 CRS incidence (P=0.90), or ICANS incidence (P=0.30).

Conclusion: Dual-targeted CAR-T cell immunotherapy demonstrates favorable efficacy and safety in RRMM. Future multicenter, large-sample studies with longer follow-up are needed to further evaluate its therapeutic potential and safety profile.

Keywords: Multiple myeloma; Refractory-relapsed multiple myeloma; Dual-targeted CAR-T cell immunotherapy; Meta-analysis

Introduction

Multiple myeloma (MM) is a malignant neoplasm characterized by clonal proliferation of plasma cells in the bone marrow, clinically manifesting as CRAB symptoms (hypercalcemia, renal insufficiency, anemia, and bone disease). MM accounts for approximately 10% of hematologic malignancies, ranking second only to lymphoma. While the introduction of proteasome inhibitors, immunomodulatory agents, autologous hematopoietic stem cell transplantation, and monoclonal antibodies has significantly improved overall survival, MM remains incurable. The pathogenesis involves high dependency

of tumor cells on the bone marrow microenvironment, with T-lymphocyte immunosuppression playing a crucial role.

Chimeric antigen receptor (CAR)-T cells are genetically modified T lymphocytes expressing an artificial CAR molecule composed of a single-chain variable fragment (scFv) targeting specific tumor antigens, CD3 signaling domain from T-cell receptors, and costimulatory structures such as CD28 or 4-1BB. This enables HLA-independent recognition and elimination of tumor cells. CAR-T cell immunotherapy has evolved through five generations: first-generation constructs contained only CD3 signaling domains; second-generation added intracellular costimulatory domains (most commonly CD28 or 4-1BB); third-generation incorporated combinations of costimulatory domains; while fourth- and fifth-generation products include intracellular domains of certain cytokine receptors, such as truncated interleukin-2 (IL-2) β-chain and STAT3-binding motifs. These iterative improvements enhance antitumor durability and reduce relapse.

BCMA (B-cell maturation antigen, also known as TNFRSF17) is a transmembrane glycoprotein highly expressed on plasma cells with minimal presence in other tissues, making it the most common target for CAR-T therapy in RRMM. Clinical trials have reported overall response rates of 80–100%, leading to FDA approval of idecabtagene and ciltacabtagene for RRMM. However, many patients still relapse with short progression-free survival, possibly due to poor CAR-T cell persistence, antigen escape, or alterations in the bone marrow microenvironment. To overcome antigen escape, expanding target coverage has been proposed to enhance CAR-T activity and improve response durability. Currently, evidence for dual-targeted CAR-T therapy in RRMM is limited to small, non-randomized early-phase trials, making it difficult to clearly understand expected toxicities and efficacy.

Methods

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered with PROSPERO (CRD42023397535).

Literature Search

We searched PubMed, Embase, Cochrane Library, Web of Science, CNKI, Wanfang, and VIP databases from inception to February 6, 2023. Chinese search terms included “多发性骨髓瘤,” “双靶点嵌合抗原受体 T 细胞,” and “双靶点 CAR-T.” English search terms included “Multiple Myeloma,” “Dual targeted,” “Combination,” “Sequential,” “bispecific,” and “Chimeric Antigen Receptor.” Reference lists of included studies were manually reviewed. The complete PubMed search strategy is shown in .

Study Selection

Two investigators independently screened literature, extracted data, and cross-verified results. Disagreements were resolved by a third reviewer. Duplicate studies were consolidated, prioritizing those with the most recent results or largest sample sizes. Inclusion criteria were: (1) patients aged >18 years with RRMM diagnosed per 2016 International Myeloma Working Group criteria; (2) treatment with dual-targeted CAR-T cells (including bispecific CAR-T or combined/sequential infusion of single-target CAR-T cells); (3) single-group rate study design; and (4) reported efficacy and safety outcomes. Exclusion criteria comprised reviews, case reports, animal studies, and studies involving newly diagnosed MM or other hematologic malignancies.

Data Extraction

Data were extracted using a customized form, including: (1) publication details (year, first author, region, DOI); (2) patient characteristics (age, high-risk cytogenetics, prior autologous stem cell transplantation [ASCT], median prior treatment lines, extramedullary disease [EMD]); (3) study features (participant number, follow-up duration); (4) CAR-T cell structural characteristics; and (5) outcome measures: primary outcomes were ORR and CRR; secondary outcomes included MRD negativity rate, EMD overall response rate, relapse rate and survival rate at last follow-up, and toxicities (CRS and ICANS).

Quality Assessment

Study quality was evaluated using the Methodological Index for Non-Randomized Studies (MINORS), which comprises 12 items (8 applicable to non-comparative studies). Each item scores 0–2 points (0=not reported, 1=reported but insufficient, 2=complete information), with a maximum score of 16. Two investigators independently performed assessments, with discrepancies resolved through consultation.

Statistical Analysis

Meta-analysis was conducted using RStudio. Effect sizes were expressed as pooled rates with 95% confidence intervals (CI) using random-effects models. Heterogeneity was assessed via subgroup analysis based on costimulatory structure, target combination, and CAR-T construct type. Sensitivity analysis evaluated result stability, and Egger's test assessed publication bias. Statistical significance was set at $P<0.05$.

Results

Literature Screening

The initial search yielded 1,320 records. After removing 463 duplicates, 857 studies remained. Title and abstract screening excluded 803 studies, leaving 54

for full-text review. Ultimately, 9 studies were included in the meta-analysis [Figure 1: see original paper]. Quality assessment results are summarized in .

Study Characteristics

All nine included studies were single-group rate studies. Eight were ongoing clinical trials, while one had been terminated. Published between 2019–2022, they included 200 participants (range: 11–62 patients per study). Patients had a median age of 18–72 years, most with high-risk cytogenetics and prior ASCT. T cells were genetically modified using γ-retroviral or lentiviral vectors. Dual-targeted CAR-T therapies were categorized into four target combinations (BCMA/CD19, BCMA/CD38, BCMA/TACI, BCMA/CS1) and two structural forms (bispecific CAR-T and combined/sequential infusion). All studies used fludarabine and cyclophosphamide for lymphodepletion. Detailed characteristics are provided in .

Efficacy Outcomes

Overall Response Rate: Nine studies reported ORR with low heterogeneity (I^2=26%, P=0.22). The pooled ORR was 90% (95%CI=0.849–0.943) [Figure 2: see original paper].

Complete Response Rate: Nine studies reported CRR with moderate heterogeneity (I^2=61%, P<0.01). The pooled CRR was 54.6% (95%CI=0.416–0.673) [Figure 3: see original paper].

MRD Negativity Rate: Five studies reported MRD negativity with high heterogeneity (I^2=85%, P<0.01). The pooled rate was 75.6% (95%CI=0.489–0.952) [Figure 4: see original paper].

EMD Overall Response Rate: Four studies reported EMD response with moderate heterogeneity (I^2=62%, P=0.05). The pooled rate was 55.1% (95%CI=0.234–0.851) [Figure 5: see original paper].

Relapse Rate at Last Follow-up: Five studies reported relapse rates with high heterogeneity (I^2=76%, P<0.01). The pooled relapse rate was 29.7% (95%CI=0.141–0.454) [Figure 6: see original paper].

Survival Rate at Last Follow-up: Six studies reported survival rates with high heterogeneity (I^2=79%, P<0.01). The pooled survival rate was 75.6% (95%CI=0.554–0.915) [Figure 7: see original paper].

Safety Outcomes

Grade 3–4 CRS: Nine studies reported grade 3–4 CRS incidence with low heterogeneity (I^2=40%, P=0.10). The pooled incidence was 16.4% (95%CI=0.094–0.245) [Figure 8: see original paper].

ICANS: Five studies reported ICANS incidence with low heterogeneity (I^2=43%, P=0.15). The pooled incidence was 4% (95%CI=0.040–0.120) [Figure 9: see original paper].

Other common adverse events included hematologic toxicities (anemia, leukopenia), infections, and hypogammaglobulinemia. Notably, 5 of 200 patients developed hemophagocytic lymphohistiocytosis (HLH), with one HLH-related death.

Subgroup Analysis

Subgroup analyses of ORR, CRR, and grade 3–4 CRS incidence were performed based on costimulatory structure, target combination, and CAR-T construct type . Results showed that 4-1BB CAR-T cells had higher ORR and CRR compared to CD28+OX40 constructs, while CD28+OX40 showed lower grade 3–4 CRS rates. Among target combinations, BCMA+CD38 demonstrated the highest CRR, while BCMA+CD19 showed the highest ORR. Combined/sequential infusion modalities exhibited higher ORR than bispecific CAR-T cells, though bispecific constructs demonstrated higher CRR and better safety profiles.

Sensitivity Analysis and Publication Bias

Sensitivity analysis confirmed the stability of all outcomes. Egger's test revealed potential publication bias for ORR (P=0.03) and EMD overall response rate (P=0.02), but no significant bias for other endpoints.

Discussion

BCMA is the most common and effective target for CAR-T therapy in MM. A previous meta-analysis by Zhang et al. reported pooled ORR of 85.2% (95%CI=0.797–0.910), CRR of 47.0% (95%CI=0.378–0.583), and MRD negativity rate of 97.8% (95%CI=0.935–1.022) for single-target BCMA CAR-T therapy, with grade 3–4 CRS incidence of 6.6% (95%CI=0.036–0.096) and ICANS incidence of 2.2% (95%CI=0.006–0.030). However, BCMA downregulation can lead to relapse, making antigen escape a critical resistance mechanism.

Dual-targeted CAR-T therapy offers a novel strategy to overcome this challenge. Since Yan et al. first reported BCMA+CD19 dual-targeted CAR-T therapy in 2017, nine clinical trials have published results, exploring four distinct target combinations. Our meta-analysis of 200 patients demonstrated an ORR of 89% (95%CI=0.83–0.94), CRR of 55% (95%CI=0.42–0.67), MRD negativity rate of 76% (95%CI=0.51–0.94), and EMD overall response rate of 55% (95%CI=0.25–0.85). The relapse rate (29.7% vs. 45%) was lower while the survival rate (74.5% vs. 84%) was modestly reduced compared to single-target BCMA CAR-T therapy.

Costimulatory structures significantly influence CAR-T cell function. CD28-based constructs exhibit rapid antitumor activity but limited persistence,

whereas 4-1BB domains enable slower but sustained expansion. CD28+OX40 costimulation reduces IL-10 release and prevents activation-induced cell death. Our analysis showed 4-1BB CAR-T cells achieved higher ORR and CRR, while CD28+OX40 constructs had lower grade 3–4 CRS rates.

Four target combinations have been investigated: BCMA/CD19, BCMA/CD38, BCMA/TACI, and BCMA/CS1. CD19 plays a crucial role in B-cell lineage differentiation, and its low expression on terminal plasma cells may contribute to resistance. Targeting both BCMA and CD19 broadens antigen coverage, eliminating diverse myeloma clones and potentially reducing BCMA escape-mediated relapse. CD38 is highly expressed on MM cells but also present on hematopoietic progenitors, requiring affinity modulation to minimize off-target effects. TACI, a TNFRSF member, mediates B-cell activation through BAFF/APRIL binding, though early trials using monomeric APRIL-based constructs showed limited efficacy. CS1 is highly expressed in MM cells and involved in myeloma-stromal cell adhesion. GPRC5D represents another promising target, with ongoing trials (NCT05509530, NCT05325801).

Dual-targeted CAR-T constructs include: (1) combined/sequential infusion, (2) bicistronic expression, (3) cotransduction, and (4) tandem bispecific CARs. Combined/sequential infusion allows flexible dosing but increases production costs, while bispecific CAR-T cells are more complex to manufacture. Our analysis showed combined/sequential infusion achieved higher ORR, whereas bispecific constructs demonstrated higher CRR and improved safety.

CRS and ICANS remain the primary toxicities. Subgroup analyses revealed that costimulatory structure, target combination, and construct type all influence CRS incidence. HLH, a rare but potentially fatal hyperinflammatory syndrome observed in approximately 1% of CAR-T recipients, may result from excessive macrophage and T-lymphocyte activation. Whether dual-targeted CAR-T increases HLH risk requires further investigation.

Beyond RRMM, dual-targeted CAR-T therapy shows promise as consolidation after ASCT in newly diagnosed MM. One study reported 100% ORR and 80% CR rate at day 100 post-ASCT, with no median PFS reached at 42 months. However, direct comparison with single-target BCMA CAR-T is limited by the single-group design of current studies. A recent trial by Garfall et al. comparing BCMA CAR-T monotherapy versus BCMA+CD19 combination in early-stage, low-burden MM found similar efficacy but lower toxicity with the combination, suggesting CD19 may be less relevant in this setting.

Limitations

First, most included studies were single-center with small samples, potentially underestimating or overestimating effect sizes. Second, insufficient data precluded pooled analysis of progression-free and overall survival, as well as subgroup analyses by risk features, prior ASCT, or CAR-T dosing. Third, eight of nine trials remain ongoing with only preliminary results reported, and no large-

scale randomized controlled trials have been published, introducing potential bias. Fourth, single-group study designs preclude direct comparison with single-target BCMA CAR-T therapy. Future RCTs are needed to confirm superiority and evaluate dual-targeted CAR-T in patients refractory to BCMA CAR-T therapy. Large-scale, high-quality evidence remains essential to support clinical application.

In conclusion, dual-targeted CAR-T cell immunotherapy demonstrates promising efficacy and safety in RRMM. Multi-target CAR-T approaches combined with novel agents may become a cornerstone of MM treatment, potentially extending survival and achieving cure.

Author Contributions: YU Haibo contributed to study design, literature search, screening, quality assessment, data extraction, statistical analysis, and manuscript writing. ZHANG Tianyu participated in literature search, screening, quality assessment, and data extraction. LI Xin, ZHANG Jiajia, SHEN Man, and ZHAN Xiaokai provided critical manuscript revisions. TANG Ran, FAN Sibin, and ZHAO Fengyi contributed to study design and methodology. HUANG Zhongxia supervised the project, provided research guidance, quality control, and English editing.

Conflict of Interest: The authors declare no conflicts of interest.

References

[1] RAJKUMAR SV. Multiple myeloma: 2022 update on diagnosis, risk stratification, and management. *Am J Hematol*. 2022;97(8):1086-1107. DOI:10.1002/ajh.26590.

[2] BRIOLI A, KLAUS M, SAYER H, et al. The risk of infections in multiple myeloma before and after the advent of novel agents: a 12-year survey. *Ann Hematol*. 2019;98(3):713-722. DOI:10.1007/s00277-019-03621-1.

[3] LAKSHMAN A, KUMAR SK. Chimeric antigen receptor T-cells, bispecific antibodies, and antibody-drug conjugates for multiple myeloma: an update. *Am J Hematol*. 2022;97(1):99-118. DOI:10.1002/ajh.26379.

[4] HONIKEL MM, OLEJNICZAK SH. Co-stimulatory receptor signaling in CAR-T cells. *Biomolecules*. 2022;12(9):1303. DOI:10.3390/biom12091303.

[5] ZHOU X, RASCHE L, KORTÜM KM, et al. BCMA loss in the epoch of novel immunotherapy for multiple myeloma: from biology to clinical practice. *Haematologica*. 2023;108(4):958-968. DOI:10.3324/haematol.2020.266841.

[6] CHOI T, KANG YB. Chimeric antigen receptor (CAR) T-cell therapy for multiple myeloma. *Pharmacol Ther*. 2022;232:108007. DOI:10.1016/j.pharmthera.2021.108007.

[7] ZAH E, NAM E, BHUVAN V, et al. Systematically optimized BCMA/CS1 bispecific CAR-T cells robustly control heterogeneous multiple myeloma. *Nat Commun*. 2020;11(1):2283. DOI:10.1038/s41467-020-16160-5.

[8] YAN ZL, CAO J, CHENG H, et al. A combination of humanised anti-CD19 and anti-BCMA CAR T cells in patients with relapsed or refractory multiple myeloma: a single-arm, phase 2 trial. *Lancet Haematol*. 2019;6(10):e521-e529. DOI:10.1016/S2352-3026(19)30115-2.

[9] RAKESH P, SONJA Z, JIM C, et al. Phase 1 first-in-human study of AUTO2, the first chimeric antigen receptor (CAR) T cell targeting APRIL for patients with relapsed/refractory multiple myeloma (RRMM). *Blood*. 2019;134(Supplement_1):3112.

[10] YAN LZ, QU S, SHANG JJ, et al. Sequential CD19 and BCMA-specific CAR T-cell treatment elicits sustained remission of relapsed and/or refractory myeloma. *Cancer Med*. 2021;10(2):563-574. DOI:10.1002/cam4.3624.

[11] JIANG H, DONG BX, GAO L. Long-term follow-up results of a multicenter first-in-human study of the dual BCMA/CD19 Targeted FasT CAR-T GC012F for patients with relapsed/refractory multiple myeloma. *J Clin Oncol*. 2021;39(15 suppl):8014-8014. DOI:10.1200/JCO.2021.39.15_{suppl}.8014.

[12] MEI H, LI CG, JIANG HW, et al. A bispecific CAR-T cell therapy targeting BCMA and CD38 in relapsed or refractory multiple myeloma. *J Hematol Oncol*. 2021;14(1):161. DOI:10.1186/s13045-021-01170-7.

[13] LI C, WANG X, WU Z, et al. p977: bispecific cs1-bcma car-t cells are clinically active in relapsed or refractory multiple myeloma. 2022.

[14] WANG Y, CAO J, GU WY, et al. Long-term follow-up of combination of B-cell maturation antigen and CD19 chimeric antigen receptor T cells in multiple myeloma. *J Clin Oncol*. 2022;40(20):2246-2256. DOI:10.1200/JCO.21.01676.

[15] TANG YY, YIN HS, ZHAO XY, et al. High efficacy and safety of CD38 and BCMA bispecific CAR-T in relapsed or refractory multiple myeloma. *J Exp Clin Cancer Res*. 2022;41(1):2. DOI:10.1186/s13046-021-02214-z.

[16] ZHANG H, LIU M, XIAO X, et al. A combination of humanized anti-BCMA and murine anti-CD38 CAR-T cell therapy in patients with relapsed or refractory multiple myeloma. 2022.

[17] ZHANG LN, SHEN XX, YU WJ, et al. Comprehensive meta-analysis of anti-BCMA chimeric antigen receptor T-cell therapy in relapsed or refractory multiple myeloma. *Ann Med*. 2021;53(1):1547-1559. DOI:10.1080/07853890.2021.1970218.

[18] VAN DER SCHANS JJ, VAN DE DONK NWCJ, MUTIS T. Dual targeting to overcome current challenges in multiple myeloma CAR T-cell treatment. *Front Oncol*. 2020;10:1362. DOI:10.3389/fonc.2020.01362.

[19] GAGELMANN N, AYUK F, ATANACKOVIC D, et al. B cell maturation antigen-specific chimeric antigen receptor T cells for relapsed or refractory multiple myeloma: a meta-analysis. *Eur J Haematol*. 2020;104(4):318-327. DOI:10.1111/ejh.13380.

[20] CAPPELL KM, KOCHENDERFER JN. A comparison of chimeric antigen receptors containing CD28 versus 4-1BB costimulatory domains. *Nat Rev Clin Oncol*. 2021;18(11):715-727. DOI:10.1038/s41571-021-00530-z.

[21] HUANG RH, LI XP, HE YD, et al. Recent advances in CAR-T cell engineering. *J Hematol Oncol*. 2020;13(1):86. DOI:10.1186/s13045-020-00910-5.

[22] HE Y, VLAMING M, VAN MEERTEN T, et al. The implementation of TNFRSF co-stimulatory domains in CAR-T cells for optimal functional activity. *Cancers*. 2022;14(2):299. DOI:10.3390/cancers14020299.

[23] LEE L, DRAPER B, CHAPLIN N, et al. An APRIL-based chimeric antigen receptor for dual targeting of BCMA and TACI in multiple myeloma. *Blood*. 2018;131(7):746-758. DOI:10.1182/blood-2017-05-781351.

[24] SCHMIDTS A, ORMHØJ M, CHOI BD, et al. Rational design of a trimeric APRIL-based CAR-binding domain enables efficient targeting of multiple myeloma. *Blood Adv*. 2019;3(21):3248-3260. DOI:10.1182/bloodadvances.2019000703.

[25] GOLUBOVSKAYA V, ZHOU H, LI F, et al. Novel CS1 CAR-T cells and bispecific CS1-BCMA CAR-T cells effectively target multiple myeloma. *Biomedicines*. 2021;9(10):1422. DOI:10.3390/biomedicines9101422.

[26] SIMON S, RIDDELL SR. Dual targeting with CAR T cells to limit antigen escape in multiple myeloma. *Blood Cancer Discov*. 2020;1(2):130-133. DOI:10.1158/2643-3230.BCD-20-146.

[27] SHAH NN, MAATMAN T, HARI P, et al. Multi targeted CAR-T cell therapies for B-cell malignancies. *Front Oncol*. 2019;9:146. DOI:10.3389/fonc.2019.00146.

[28] ZHANG XM, ZHU LL, ZHANG H, et al. CAR-T cell therapy in hematological malignancies: current opportunities and challenges. *Front Immunol*. 2022;13:927153. DOI:10.3389/fimmu.2022.927153.

[29] SHI XL, YAN LZ, SHANG JJ, et al. Anti-CD19 and anti-BCMA CAR T cell therapy followed by lenalidomide maintenance after autologous stem-cell transplantation for high-risk newly diagnosed multiple myeloma. *Am J Hematol*. 2022;97(5):537-547. DOI:10.1002/ajh.26486.

[30] GARFALL AL, COHEN AD, SUSANIBAR-ADANIYA SP, et al. Anti-BCMA/CD19 CAR T cells with early immunomodulatory maintenance for multiple myeloma responding to initial or later-line therapy. *Blood Cancer Discov*. 2023;4(2):118-133. DOI:10.1158/2643-3230.BCD-22-0074.

Note: Figure translations are in progress. See original paper for figures.