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BCMA/GPRC5D bispecific CAR T-cell therapy for relapsed/refractory multiple myeloma with extramedullary disease: a single-center, single-arm, phase 1 trial

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Abstract

Relapsed/refractory multiple myeloma (RRMM) with extramedullary disease (EMD) represents a challenging condition, with limited treatment options and poor prognosis. We conducted a phase 1 clinical trial to evaluate the safety and effectiveness of a novel bispecific chimeric antigen receptor (CAR) T-cell therapy targeting two antigens, B-cell maturation antigen and G protein-coupled receptor class C group 5 member D (BCMA/GPRC5D), in this high-risk population. A total of 12 patients were enrolled, of whom 3 were excluded due to disease progression or death before CAR T-cell infusion, despite meeting the inclusion criteria, leaving 9 for analysis. The median follow-up was 6.08 months (Interquartile Range [IQR]: 0.9–16.5). All patients received BCMA/GPRC5D bispecific CAR T-cell therapy after bridging therapy with localized radiotherapy or Elranatamab. Efficacy assessments revealed that 100% of patients achieved partial response (PR) or better, with 44.4% achieving complete response (CR). Common adverse events included hematological toxicities such as anemia, leukopenia, and thrombocytopenia. Cytokine release syndrome (CRS) occurred in 66.7% of patients, all of which were grade 1–2, and no neurotoxicity (ICANS) was observed. The 1-year overall survival (OS) and progression-free survival (PFS) rates were 60% and 63%, respectively. Median OS and PFS were not reached. Collectively, these findings highlight a potential therapeutic strategy involving BCMA/GPRC5D dual-targeted CAR T-cell therapy for patients with aggressive forms of multiple myeloma, particularly those with extramedullary disease, and support the need for further exploration and validation in larger, multi-center clinical studies.

Keywords BCMA, GPRC5D, CAR T-cell therapy, Relapsed/refractory multiple myeloma, Extramedullary disease, Immunotherapy

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To The Editor

We report on a Phase I clinical trial assessing the safety and efficacy of B-cell maturation antigen and G protein-coupled receptor class C group 5 member D (BCMA/GPRC5D) bispecific CAR T-cell therapy in patients with relapsed/refractory multiple myeloma (RRMM) and extramedullary disease (EMD). Despite significant advancements, including proteasome inhibitors, immunomodulatory agents, and monoclonal antibodies such as daratumumab, outcomes for RRMM, especially those with EMD, remain suboptimal [1, 2]. EMD, characterized by clonal plasma cells infiltrating tissues outside the bone marrow, confers a poor prognosis and increased resistance to standard therapies [1, 3, 4]. Moreover, single-antigen-targeted immunotherapies such as BCMA CAR T-cell therapies, while groundbreaking, face challenges such as antigen escape and tumor heterogeneity, limiting durable responses for this population [5–7].

Dual-targeting CAR T-cell therapies offer a promising alternative to address antigenic escape and therapeutic resistance. BCMA remains the most established target in MM due to its universal expression in plasma cells, but resistance often arises due to downregulation or loss of antigen during treatment [3, 7, 8]. The addition of GPRC5D as a secondary target introduces a novel approach to circumvent antigen escape [9, 10]. GPRC5D is highly expressed on myeloma cells and exhibits minimal expression on normal tissues, making it an ideal secondary target for combination CAR T-cell receptor designs [10, 11]. Early studies have demonstrated the feasibility and efficacy of BCMA/GPRC5D bispecific CAR T-cell constructs in preclinical and early-phase trials, with dual targeting showing enhanced tumor control compared to single-target CAR T cells [10–12].

This trial enrolled 12 patients with RRMM and EMD from July 2023 to September 2024. Of the 12 eligible patients, 3 died from rapid disease progression before receiving CAR T-cell therapy and were excluded from efficacy analysis. The intention-to-treat (ITT) response rate was 75% (9/12), and the per-protocol (PP) response rate was 100% (9/9). The cohort had a median age of 62 years, with 62% being female. These patients had a median of three prior therapy lines, with 46% having undergone autologous stem cell transplantation (ASCT). Fifty percent of patients had high-risk cytogenetic abnormalities, including del(17p), t(4;14), or t(14;16), and 19%

Table 1 Baseline characteristics of patients enrolled in BCMA/GPRC5D CAR T-cell therapy trial

Baseline Characteristics	*N* = 9(%)
Age, years	64 (48–80) (N/A)
Male	4 (44.4)
Female	5 (55.6)
Time of CART treatment after diagnosis, months	48 (7–160) (N/A)
Monoclonal globulin IgG	4 (44.4)
Monoclonal globulin IgA	4 (44.4)
Monoclonal globulinIgD	1 (11.1)
Light chain	1 (11.1)
Non secretory	0 (0.0)
High-risk cytogenetic profile	6 (66.7)
High tumor burden	9 (100.0)
R-ISS I	0 (0.0)
R-ISS II	2 (22.2)
R-ISS III	7 (77.8)
EMD	9 (100.0)
Renal dysfunction	2 (22.2)
Previous treatment line > 3	8 (88.9)
Previous BCMA CAR-T treatment	0 (0.0)
Previous ASCT treatment	2 (22.2)
Therapeutic target BCMA-GPRC5D	9 (100.0)

Abbreviations: *IgG* Immunoglobulin G, *IgA* Immunoglobulin A, *IgD* Immunoglobulin D, *EMD* Extramedullary Disease, *R-ISS* Revised International Staging System, *ASCT* Autologous Stem Cell Trasplant

(See figure on next page.)

Fig. 1 Clinical Responses, CAR T-Cell Expansion, Survival, Adverse Events, and Inflammatory Markers in Patients Treated with BCMA/GPRC5D Dual Targeted CAR T-Cells. **A** Overall Response Rate (ORR) and Individual Patient Responses. The left bar chart shows the overall response rate (ORR), with 100% of patients (9/9) achieving clinical response (PR, VGPR, or CR). The right panel shows individual patient responses: each bar represents the duration of response (in days) for each patient, with different colors indicating the best response: Complete Response (CR) in green, Very Good Partial Response (VGPR) in pink, Partial Response (PR) in blue, and Progressive Disease (PD) in red. Data points indicate patient response status during the follow-up period. **B** CAR T-Cell Expansion in Peripheral Blood. The number of CAR T-Cells (cells/μL) in peripheral blood is shown for each patient across different time points post-infusion. Lines represent individual patient data, with each color corresponding to a different patient. **C** Overall Survival (OS) and Progression-Free Survival (PFS). Kaplan–Meier survival curves depicting the overall survival (OS, top) and progression-free survival (PFS, bottom) of patients following BCMA/GPRC5D dual-targeted CAR T-Cell infusion. **D** Adverse Events (AEs). A horizontal bar plot showing the incidence of various adverse events (AEs) observed in patients post-treatment, grouped by severity (Grade 1–2, blue and Grade 3–4, light blue). The left side represents CAR T-related AEs, and the right side represents all AEs, both collected from the same patient cohort. This mirrored design facilitates direct comparison between the two categories. The listed AEs include neutropenia, leukopenia, hypokalemia, anemia, hypocalcemia, lymphopenia, CRS, elevated AST/ALT, abdominal pain, infection, and others. Each bar represents the percentage of patients experiencing each event. Abbreviations: ORR = Overall Response Rate, CR = Complete Response, VGPR = Very Good Partial Response, PR = Partial Response, PD = Progressive Disease, OS = Overall Survival, PFS = Progression-Free Survival, AEs = Adverse Events, CRS = Cytokine Release Syndrome

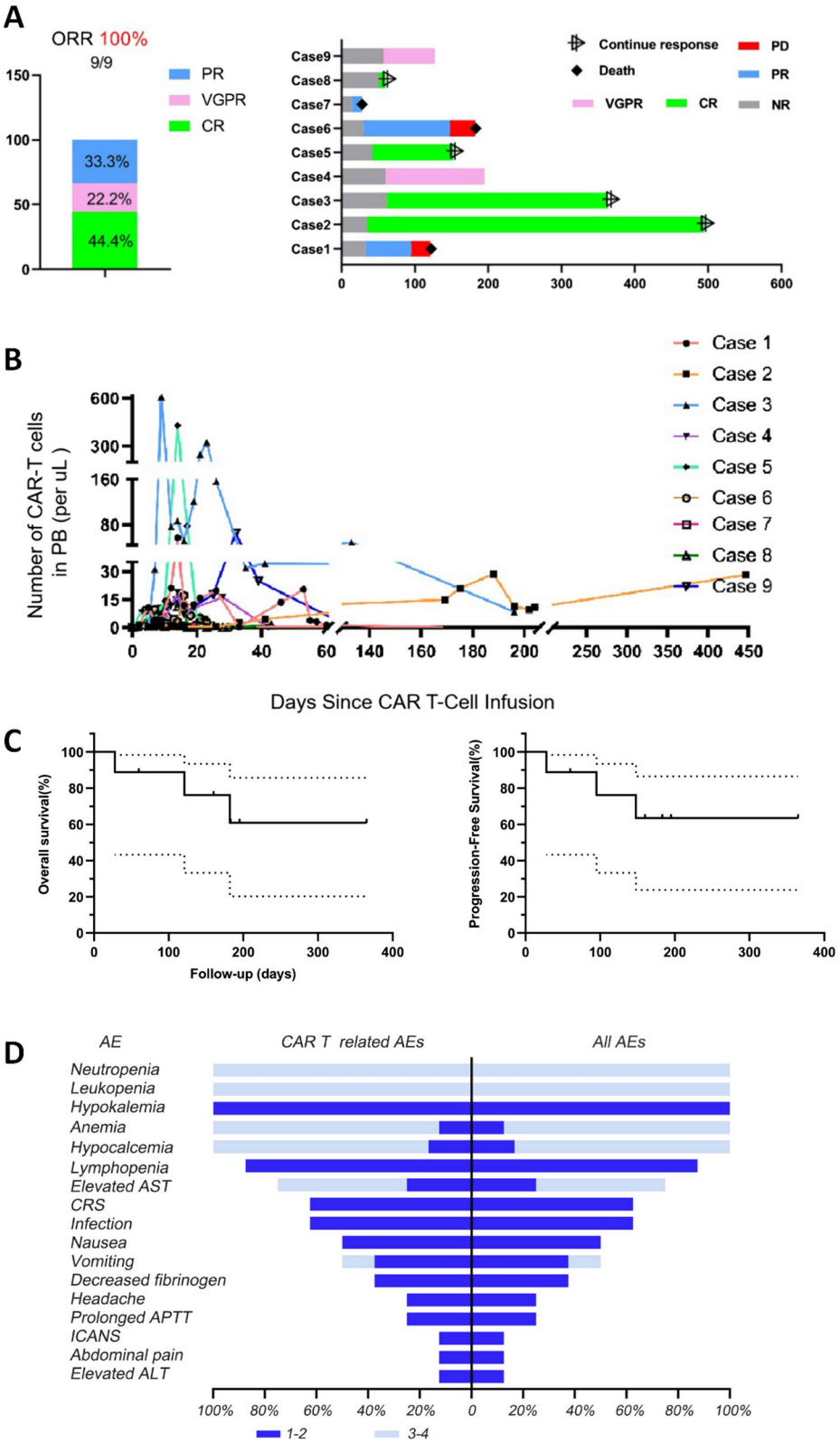

Fig. 1 (See legend on previous page.)

had extramedullary disease. Notably, 71% were refractory to proteasome inhibitors, 75% to lenalidomide, and 62% to CD38 antibodies (Table 1).

After leukapheresis, two patients with bulky extramedullary disease received bridging therapy to reduce tumor burden prior to lymphodepletion—one with Elranatamab alone (7 mg/kg daily for 5 days, starting 10 days before CAR T-cell infusion), and the other with the same Elranatamab regimen combined with localized radiotherapy (180 cGy ×10 fractions). All patients subsequently received BCMA/GPRC5D bispecific CAR T-cell therapy. The lymphodepletion regimen consisted of cyclophosphamide and fludarabine. One patient received a higher dose of 1.5×10^6 cells/kg, while the remaining patients received 1.0×10^6 cells/kg. The primary endpoints were safety and efficacy, with secondary endpoints including CAR T-cell expansion, clinical responses, and measurable residual disease (MRD) (Supplemental Fig. 1). The study aimed to address the unmet needs of this heavily pretreated, high-risk patient population, providing new therapeutic options.

The clinical response rate was promising, with an overall response rate (ORR) of 100%. Among the nine patients, 44.4% achieved complete response (CR), 22.2% achieved very good partial response (VGPR), and 33.3% achieved partial response (PR) (Fig. 1A). However, two patients progressed after an initial response, and one patient died from disease progression. CAR T-cell dynamics revealed rapid expansion, with peak levels occurring between days 10 and 14. CAR T-cell persistence varied, with some patients maintaining detectable CAR T-cells for over 400 days, correlating with deeper and more durable responses (Fig. 1B). The median follow-up was 6.08 months (Interquartile Range [IQR]: 0.9–16.5). The Kaplan–Meier survival analysis showed a 12-month overall survival (OS) rate of 60% and a progression-free survival (PFS) rate of 63%. The median OS and PFS had not yet been reached at the time of analysis, suggesting a potential for durable therapeutic benefit (Fig. 1C). Importantly, extramedullary disease (EMD) also responded, with complete resolution in four cases and partial shrinkage in five (Supplemental Fig. 2, Supplemental Fig. 3).

The safety profile was consistent with CAR T-cell therapies. Hematological toxicities, including leukopenia, neutropenia, and anemia, were common, with 88.9% of patients developing thrombocytopenia. Cytokine release syndrome (CRS) occurred in 66.7% of patients, mostly grade 1–2, and neurotoxicity (ICANS) was observed in 11.1%. As shown in Fig. 1D, adverse events (AEs) are presented in a mirrored horizontal bar chart comparing CAR T-related AEs (left) and all AEs (right), both derived from the same patient cohort. This layout facilitates intuitive visual comparison and does not imply two distinct populations. These adverse events were manageable, and the safety profile remained consistent with known CAR T-cell therapy risks [7, 8, 11]. Adverse events are summarized in Supplemental Table 1.

Inflammatory markers, including IL-6, CRP, and ferritin, were transiently elevated following infusion, peaking at median times of 10, 8.5, and 12 days, respectively. These changes were self-limiting and resolved without significant complications, supporting the manageable nature of cytokine release and immune activation following treatment (Supplemental Fig. 4).

The limitations of our study include its small sample size, single-center design, and relatively short follow-up period, as well as the lack of a direct comparison with single-target CAR T-cell therapies. Larger, multicenter trials with extended follow-up are needed to validate our results and more clearly define the role of BCMA/GPRC5D bispecific CAR T-cell therapy in the treatment of relapsed/refractory multiple myeloma with extramedullary disease.

Taken together, BCMA/GPRC5D bispecific CAR T-cell therapy demonstrates a high response rate, encouraging survival outcomes, and a manageable safety profile, making it a valuable treatment option for this high-risk patient population. These findings highlight the need for further investigation of dual-target CAR T-cell approaches to address the unmet clinical needs in patients with extramedullary disease.

Abbreviations

RRMM	Relapsed/Refractory Multiple Myeloma
EMD	Extramedullary Disease
CAR T-cell	Chimeric Antigen Receptor T-cell
BCMA	B-cell Maturation Antigen
GPRC5D	G Protein-Coupled Receptor Class C Group 5 Member D
PP	Per-Protocol
ITT	Intent-to-Treat
ASCT	Autologous Stem Cell Transplantation
IQR	Interquartile Range
CR	Complete Response
VGPR	Very Good Partial Response
PR	Partial Response
OS	Overall Survival
PFS	Progression-Free Survival
CRS	Cytokine Release Syndrome
ICANS	Immune Effector Cell-Associated Neurotoxicity Syndrome
MRD	Measurable Residual Disease

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

Supplementary Material 5.

Supplementary Material 6.

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Authors' contributions
FY.F. and H.Y. conceived and designed the study and drafted the manuscript. AH.C. and Y.S. provided technical guidance in study design and methodology. SH.R., LH.W., MQ.R., and L.Q. conducted clinical assessments and data collection. J.C., D.C., Y.H., MJ.L., and BT.D. were involved in data collection and analysis. YL.L. and YL.C. contributed to methodology and validation. SH.L. managed clinical care for two patients included in the study. All authors contributed to the interpretation of the results and reviewed and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of People's Liberation Army The General Hospital of Western Theater Command (Approval Number: 2024EC1-ky033). All experiments were conducted in compliance with relevant ethical guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
Declaration of interests AHC is a founding member of Shanghai YaKe Biotechnology, a biotechnology company focusing on research and development of tumour cellular immunotherapy. All other authors declare no competing interests.

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