Efficacy and safety of chimeric antigen receptor T-cell therapy for plasma cell leukemia

Plasma cell leukemia (PCL) can be primary or secondary, the latter arising from leukemia transformation of plasma cell myeloma.[1] Chimeric antigen receptor (CAR) T-cell therapy is effective in plasma cell myeloma.[2-4] Because PCL shares the same origin as plasma cell myeloma, we determined whether CAR T-cell therapy might also be effective in PCL. This study complied with the Declaration of Helsinki and Good Clinical Practice guidelines. It was approved by the Institutional Review Board/Ethics Committee, and all patients provided written informed consent.

Subjects were 18-70 years with PCL, according to International Myeloma Working Group (IMWG) criteria, had a Karnofsky performance score (KPS) ≥50, life expectancy >12 weeks and no contraindications to the proposed treatment.[5] The trial is registered at chictr.org.cn with numbers ChiCTR2100048888 and ChiCTR-OIC-17011272.

Lymphocytes were isolated using a blood cell separator and $CD3^+$ T cells were sorted and activated using anti-CD3/CD28 immunomagnetic beads (CTS™ Dynabeads™ CD3/D28, Gibco, Grand Island, NY, USA). The anti-B-cell maturation antigen (BCMA) and G protein-coupled receptor, class C group 5 member D (GPRC5D)-targeted CAR constructs, consisting of a scFv, CD8α hinge/transmembrane, 4-1BB, and CD3ζ domains, were cloned into lentiviral vectors. While the GPRC5D scFv originated from a phage display library, the BCMA scFv was humanized and linked to an EGFRt reporter via a T2A sequence. For manufacturing, patient-derived $CD3^+$ T cells were transduced with the respective lentivirus, and expanded i*n vitro* for subsequent use. Subjects received cyclophosphamide, 750 mg/m^2 on day −5; fludarabine 30 mg/m^2/day on days −5 to −3 and the CAR T-cell infusion on day 0.

Efficacy evaluations included overall response rate, stringent complete response, complete response, very good partial response and partial response based on the IMWG criteria.[5] Progression-free survival was defined as the interval from CAR T-cell infusion to progression or death from any cause. Survival was defined as the interval from CAR T-cell infusion to death from any cause. Duration of response was defined as the interval from best response to progression or death from any cause. Bone marrow aspirates were analyzed for measurable residual disease using the EuroFlow

Table 1. Baseline characteristics of the patients (N=11) with plasma cell leukemia.

Characteristic	Values
Age, years, median (IQR)	54 (44-61)
PCL type, N (%)	
Primary	4 (36)
Secondary	7 (64)
Sex, N (%)	
Female	4 (36)
Male	7 (64)
Type of myeloma, N (%)	
IgG-κ	4 (36)
IgA-λ	2 (18)
Light chain	1 (9)
IgD-λ	3 (27)
Non-secretory	1 (9)
R-ISS disease stage, N (%)	
II	4 (36)
III	7 (64)
Karnofsky Performance Score, N (%)[a]	
50-60	2 (18)
70-80	8 (73)
90-100	1 (9)
High tumor burden, N (%)[b]	7 (64)
Soft tissue involvement, N (%)	4 (36)
Complex chromosomal karyotypes, N (%)	5 (45)
Renal impairment, N (%)	2 (18)
Previous lines of therapy	
Number, median (IQR)	4 (2-5)
≥3, N (%)	7 (64)
Previous therapies, N (%)	
Proteasome inhibitors	
Bortezomib	11 (100)
Ixazomib	2 (18)
Carfilzomib	5 (45)
Immunomodulatory drugs	
Lenalidomide	11 (100)
Pomalidomide	7 (64)
Anti-CD38 monoclonal antibodies	7 (64)
Previous ASCT	7 (64)
Previous allo-HSCT	1 (9)
Other	
Selinexor	4 (36)
Venetoclax	1 (9)

Baseline assessments were performed prior to lymphodepleting chemotherapy. No patient had a history of treatment with BCMA- or GPRC5D-targeted agents (including bispecific T-cell engagers or antibody-drug conjugates). [a]Karnofsky Performance Scores range from 0 to 100, with lower scores indicating greater disability and a score of 0 indicating death. [b]High tumor burden was defined as at least 50% clonal plasma cells or bone marrow plasma cells. IQR: interquartile range; PCL: plasma cell leukemia; Ig: immunoglobulin; R-ISS: Revised International Staging System; ASCT: autologous stem cell-transplantation; allo-HSCT: allogeneic hematopoietic stem cell transplantation.

standardized protocol (sensitivity threshold: 10^{-5}).[6]

Adverse events including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded using American Society for Transplantation and Cellular Therapy (ASTCT) criteria and severity scored using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.[7,8]

The data cutoff date was March 2025. Eleven subjects were enrolled between June 2020 and March 2025. Four had primary PCL and seven had secondary PCL. There were seven men and the median age was 54 years (interquartile range [IQR], 44-61 years). The subjects had stage II or III disease according to the Revised International Staging System. The median number of prior therapies was 4 (IQR, 2-5). Seven subjects had had a prior autologous hematopoietic cell transplant and one, an allotransplant. None of the enrolled patients had previously received any BCMA- or GPRC5D-targeted therapies, including bispecific T-cell engagers (e.g., bispecific antibodies) or antibody-drug conjugates. Four subjects had soft tissue involvement and five had complex cytogenetic abnormalities defined as ≥3 clonal abnormalities[9,10] (Table 1).

All subjects had CRS, including eight (73%) who had grade 1 and three (27%) who had grade 2 CRS (Table 2). The median duration of CRS was 5 days (IQR, 4-5 days). Management included tocilizumab and corticosteroids. All subjects had transient increases in serum interleukin-6 and ferritin. One subject had grade 2 ICANS. All subjects had grade >2 hematologic adverse events and late immune effector cell-associated hematotoxicity, predominantly grades 1 and 2.[11]

All subjects responded to the CAR T-cell therapy (*Online Supplementary Table S1*). The best responses were stringent complete response (N=3), complete response (N=4), very good partial response (N=1) and partial response (N=3) (Figure 1A). Of the five patients with a complex karyotype, four obtained a very good partial response or better. Only one of four patients with soft tissue involvement achieved a complete response. Two of three subjects with a partial response had soft tissue involvement. All subjects had a bone marrow negative measurable residual disease test by day 28. The failure to attain a stringent complete response despite achieving measurable residual disease negativity might be linked to extramedullary disease or specific genetic profiles (*Online Supplementary Figure S1*). The median progression-free survival was 290 days (95% confidence interval [95% CI]: 90 days - not reached, but must exceed 420 days) (Figure 1B). The median survival was 320 days (95% CI: 120 days - not reached, but must exceed 690 days) (Figure 1C). Four patients remained progression-free after CAR T-cell therapy, and seven patients experienced recurrence during the follow-up period. Five of seven subjects who progressed received a second CAR T-cell infusion and all of these achieved a partial response or better, of whom three patients survived over 600 days. (*Online Supplementary Table S1*).

Our study advances beyond comparative analyses of anti-BCMA CAR T-cell therapy by prospectively evaluating a salvage regimen incorporating both anti-BCMA and anti-GPRC5D CAR T-cell products.[12] Furthermore, it provides pioneering clinical data demonstrating the feasibility and efficacy of this strategy, which involves intentional target switching upon relapse after prior CAR T-cell therapy. Seven subjects died, due to disease progression (N=5), graft-*versus*-host disease after an allotransplant (N=1), and hemorrhage (N=1; patient 6 died from massive hemoptysis [pulmonary hemorrhage] secondary to severe, grade 4 thrombocytopenia 4 months after the infusion).

Here, we report on a cohort of 11 subjects with advanced primary or secondary PCL who were treated with CAR T-cell therapy targeting either BCMA or GPRC5D. All patients exhibited a clinical response to treatment, with seven individuals achieving a complete response, underscoring the substantial antitumor activity of CAR T cells in this aggressive hematologic malignancy. Notably, among those patients who experienced disease relapse, five responded favorably to a second CAR T-cell infusion, suggesting that repeated administration may recapture clinical benefit and extend disease control in selected cases. These findings position CAR T-cell therapy as a promising and potentially transformative therapeutic option for PCL, a condition historically associated with limited treatment alternatives and poor outcomes.

This study included patients with both primary PCL and secondary PCL. Despite the limitation of a small sample size, subgroup analysis suggested divergent survival outcomes following CAR T-cell therapy. Patients with primary PCL achieved a median progression-free survival of 345 days, compared to 120 days for those with secondary PCL. Similarly, the median survival was 375 days for patients with primary PCL and 300 days for those with secondary PCL (*Online Supplementary Figure S2*). These trends are concordant with the established biological heterogeneity and differential clinical prognosis between the two disease subtypes. Although the differences did not reach statistical significance in this limited cohort, they emphasize the necessity of evaluating primary PCL and secondary PCL as distinct entities in future, larger-scale studies to delineate treatment efficacy and prognostic determinants more precisely.

Our data suggest that CAR T cells are a potential therapy for PCL. To our knowledge, only a limited number of similar clinical experiences have been documented in the literature, as referenced in prior reports,[13-15] highlighting the novelty and importance of the present analysis. Nevertheless, our study has several limitations that warrant consideration. First, the small sample size may limit the generalizability of the conclusions and preclude robust subgroup analyses. Second, heterogeneity in patients' characteristics, and prior treatment histories introduces potential confounding

Table 2. Adverse events.

Adverse events	Patient N										
	1	2*	3	4*	5*	6	7	8*	9*	10	11
CRS[a]	1	1	1	1	2	1	2	1	1	2	1
ICANS[a]	No	No	No	No	No	No	No	2	No	No	No
Hematologic											
Leukopenia	4	4	4	4	3	4	3	3	4	3	4
Neutropenia	3	3	4	4	3	3	3	3	4	2	4
Anemia	3	3	3	4	3	3	3	3	3	3	4
Thrombocytopenia	4	4	4	3	4	4	3	4	4	4	4
Early ICAHT (day 0-30)	III	III	II	II	II	III	II	I	II	I	II
Late ICAHT (after day 30)	I	II	I	I	II	II	I	I	I	I	I
B-cell aplasia (months)	Yes (10)	Yes (2)	Yes (2)	Yes (12+)	Yes (2)	Yes (3)	Yes (2.5)	Yes (3)	No	Yes (4)	Yes (2+)
Hypogammaglobulinemia[b]	No	Yes	No	Yes	No	No	Yes	No	No	No	No
Infections											
Any infection	Yes	Influenza A virus	No	No	Influenza A virus	Yes	Yes	COVID-19	No	Fungal	Influenza A virus
Lung infection	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes
Other											
Renal toxicity	No	No	No	No	No	No	No	No	No	No	No
Hypofibrinogenemia	Yes	No	Yes	No	No	No	Yes	Yes	No	Yes	No
Prolonged APTT	Yes	No	No	No	No	No	No	No	No	No	No
Increased AST	No	No	No	Yes	Yes	No	Yes	Yes	No	No	No
Increased ALT	No	No	No	Yes	Yes	No	Yes	No	No	No	No

The numbers 1-4 and I-III indicate the grade of severity of the adverse event. Hematologic toxicities were graded according to Common Terminology Criteria for Adverse Events version 5.0. *Patients who, after relapsing following initial chimeric antigen receptor (CAR) T-cell therapy, received a second infusion of CAR T cells targeting a different antigen. [a]CRS and ICANS were graded according to the American Society for Transplantation and Cellular Therapy consensus criteria. [b]Hypogammaglobulinemia was defined as an IgG level <400 mg/dL. CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome; ICAHT: immune effector cell associated hematotoxicity; COVID-19: coronavirus disease 2019; APTT: activated partial thromboplastin time; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

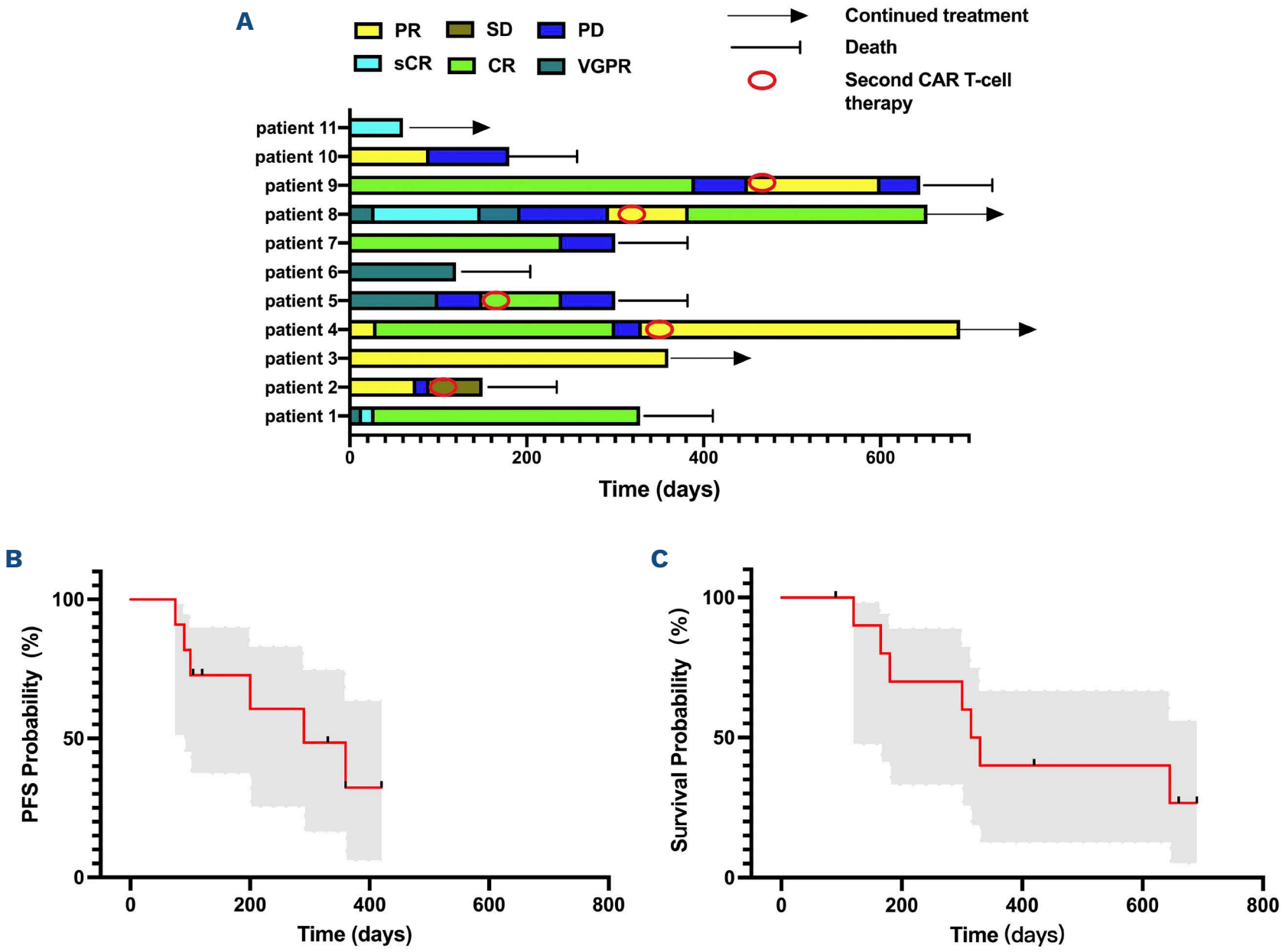


Figure 1. Clinical outcomes of patients with plasma cell leukemia treated with chimeric antigen receptor T-cell therapy. (A) Response durations following the first chimeric antigen receptor T-cell therapy. Each bar represents one subject in this study. (B, C) Kaplan–Meier estimates of progression-free survival (B) and survival (C). The shaded area indicates the 95% confidence interval. PR: partial response; SD: stable disease; PD: progressive disease; sCR: stringent complete response; CR: complete response; VGPR: very good partial response; CAR: chimeric antigen receptor; PFS: progression-free survival.

factors. Third, the relatively brief follow-up period restricts the ability to assess long-term efficacy. Therefore, while our results are encouraging, further validation is essential through larger, prospective, and ideally multicenter clinical trials designed to evaluate CAR T-cell therapy in homogeneous PCL populations, with longer follow-up and comprehensive correlative studies to identify predictive biomarkers and optimize treatment strategies.

Authors

Chenyuan Hu,[1-3*] Na Qi,[1*] Wei Wang,[1,4*] Robert Peter Gale,[5] Feng Zhu,[1] Hujun Li,[1] Hai Cheng,[1] Jiang Cao,[1] Zhiling Yan,[1] Kunming Qi,[1] Wei Sang,1 Kai Zhao[1-3,6] and Wei Chen[1-3]

[1]Department of Hematology, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, China; [2]Blood Diseases Institute, Xuzhou Medical University, Xuzhou, China; [3]Key Laboratory of Bone Marrow Stem Cells, Xuzhou Medical University, Xuzhou, China; [4]Department of Cardiology, The Affiliated Sihong Hospital of Xuzhou Medical University, Xuzhou, China; [5]Haematology Research Centre, Department of Immunology and Inflammation, Imperial College London, London, UK and [6]Technology Innovation and Public Service Center, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, China

**CH, NQ and WW contributed equally as first authors.*

Correspondence:
W. CHEN - feihu0808@163.com
K. ZHAO - kainyzhao@163.com

https://doi.org/10.3324/haematol.2026.000001

Received: January 3, 2026.
Accepted: March 11, 2026.
Early view: March 19, 2026.

©2026 Ferrata Storti Foundation

Published under a CC BY-NC license

Disclosures

RPG is a consultant to Antengene Biotech LLC and Shenzen TargetRx; is Medical Director of FFF Enterprises Inc.; is a speaker for Janssen Pharma, BeiGene and Hengrui Pharma; sits on the Board of Directors of the Russian Foundation for Cancer Research Support and is a member of a scientific advisory board for StemRad Ltd. The other authors have no conflicts of interest to disclose.

Contributions

CH, KZ, and WC conceived and designed the study. CH, NQ, ZY, JC, HC, WS, FZ, and KQ provided study materials or patients. CH, WW, WC, JC, HC, WS, and FZ collected and assembled data. CH, NQ, WW, and WC analyzed and interpreted data. CH, RPG, KZ, and WC wrote the typescript. All authors approved the typescript, accept responsibility for its content and agreed to submit it for publication.

Funding

This study was supported, in part, by Jiangsu Province High-Level Hospital Construction Project (SHJDBF2024210, LCZX202512, GSPJS202417, GSPJS202420, GSPJS202414), the National Natural Science Foundation of China (grant number 82341203), and the National Key Clinical Specialty Construction Program, Medical Research Foundation of Jiangsu Provincial Health Commission (M2024059). RPG receives support from the UK National Institute of Health Research (NIHR).

Data-sharing statement

De-identified data are available upon reasonable request to the corresponding author.

References

1. Saba L, Landau KS, Liang H, et al. Real world analysis on the determinants of survival in primary plasma cell leukemia in the United States. Leukemia. 2024;38(2):435-437.
2. Munshi NC, Anderson LD Jr, Shah N, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. N Engl J Med. 2021;384(8):705-716.
3. Mailankody S, Devlin SM, Landa J, et al. GPRC5D-targeted CAR T cells for myeloma. N Engl J Med. 2022;387(13):1196-1206.
4. Wang Y, Hu X, Du J, et al. CAR-T cell therapy for patients with extramedullary multiple myeloma opportunities and challenges. Eur J Cancer. 2025;220:115374.
5. Fernández de Larrea C, Kyle RA, Durie BG, et al. Plasma cell leukemia: consensus statement on diagnostic requirements, response criteria and treatment recommendations by the International Myeloma Working Group. Leukemia. 2013;27(4):780-791.
6. van Dongen JJ, Lhermitte L, Bottcher S, et al. EuroFlow antibody panels for standardized n-dimensional flow cytometric immunophenotyping of normal, reactive and malignant leukocytes. Leukemia. 2012;26(9):1908-1975.
7. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019;25(4):625-638.
8. Freites-Martinez A, Santana N, Arias-Santiago S, et al. Using the Common Terminology Criteria for Adverse Events (CTCAE - Version 5.0) to evaluate the severity of adverse events of anticancer therapies. Actas Dermosifiliogr (Engl Ed). 2021;112(1):90-92.
9. Nguyen-Khac F, Bidet A, Daudignon A, et al. The complex karyotype in hematological malignancies: a comprehensive overview by the Francophone Group of Hematological Cytogenetics (GFCH). Leukemia. 2022;36(6):1451-1466.
10. Uryu H, Mishima Y, Ishihara Y, et al. Complex karyotype determined using conventional cytogenetic analysis is a poor prognostic factor in patients with multiple myeloma. J Clin Exp Hematop. 2024;64(1):10-20.
11. Rejeski K, Subklewe M, Aljurf M, et al. Immune effector cell-associated hematotoxicity: EHA/EBMT consensus grading and best practice recommendations. Blood. 2023;142(10):865-877.
12. Galarza Fortuna GM, Peres L, Nazarenko E, et al. Safety and efficacy of BCMA-directed chimeric antigen receptor T-cell therapy for the treatment of plasma cell leukemia. Blood Adv. 2025;9(23):6009-6018.
13. Li C, Cao W, Que Y, et al. A phase I study of anti-BCMA CAR T cell therapy in relapsed/refractory multiple myeloma and plasma cell leukemia. Clin Transl Med. 2021;11(3):e346.
14. Wang D, Wang J, Hu G, et al. A phase 1 study of a novel fully human BCMA-targeting CAR (CT103A) in patients with relapsed/refractory multiple myeloma. Blood. 2021;137(21):2890-2901.
15. Sidana S, Patel KK, Peres LC, et al. Safety and efficacy of standard-of-care ciltacabtagene autoleucel for relapsed/refractory multiple myeloma. Blood. 2025;145(1):85-97.