haematologica
Journal of the Ferrata Storti Foundation

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Received: January 3, 2026.
Accepted: March 11, 2026.

Citation: Chenyuan Hu, Na Qi, Wei Wang, Robert Peter Gale, Feng Zhu, Hujun Li, Hai Cheng, Jiang Cao, Zhiling Yan, Kunming Qi, Wei Sang, Kai Zhao and Wei Chen. Efficacy and safety of chimeric antigen receptor T-cell therapy for plasma cell leukemia.
Haematologica. 2026 Mar 19. doi: 10.3324/haematol.2026.000001 [Epub ahead of print]

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

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Disclosures

RPG is a consultant to Antengene Biotech LLC; Consultant Shenzen TargetRx; Medical Director, FFF Enterprises Inc.; A speaker for Janssen Pharma, BeiGene and Hengrui Pharma; Board of Directors: Russian Foundation for Cancer Research Support and Scientific Advisory Board, StemRad Ltd.

Acknowledgement

RPG acknowledges support from the UK National Institute of Health Research (NIHR).

Contributions

Conception and design: CYH, KZ, WC. Provision of study materials or patients: CYH, NQ, ZLY, JC, HC, WS, FZ, KMQ. Collection and assembly of data: CYH, WW, WC, JC, HC, WS, FZ. Data analysis and interpretation: CYH, NQ, WW, WC. Writing: CYH, RPG, KZ, WC. The authors approved the typescript, accept responsibility for the content and agreed to submit for publication

Funding

Supported, in part, by Jiangsu Province High-Level Hospital Construction Project (SHJDBF2024210, LCZX202512, GSPJS202417, GSPJS202420, GSPJS202414), National Natural Science Foundation of China (Grant No. 82341203), National Key Clinical Specialty Construction Program, Medical Research Foundation of Jiangsu Provincial Health Commission (M2024059).

Data-Sharing Statement

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

Running head: CAR T therapy in patients with R/R PCL.

Word count: 1217 (1,500 max)
Tables/Figures: 2/1 (4 max)
References: 15 (15 max)

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Plasma cell leukemia (PCL) can be primary or secondary (sPCL), the latter arising from leukemia transformation of plasma cell myeloma (PCM) [1]. Chimeric antigen receptor (CAR) T-cell therapy is effective in PCM [2-4]. Because PCL shares the same origin as PCM, 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 using International Myeloma Working Group (IMWG) criteria, Karnofsky performance score (KPS) ≥ 50, life expectancy > 12 weeks and no contraindications.[5] The trial is registered at chictr.org.cn (ChiCTR2100048888) and (ChiCTR-OIC-17011272).

Lymphocytes were isolated using a blood cell separator and CD3-positive T-cells 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 in vitro for subsequent use. Subjects received cyclophosphamide, 750 mg/mE+2/d, day −5; fludarabine 30 mg/mE+2/d, days −5 to −3 and CAR T cells infusion on day 0.

Efficacy was evaluated with including overall response rate, stringent complete response (sCR), complete response (CR), very good partial response (VGPR) and partial response (PR) based on the IMWG criteria [5]. Progression-free survival (PFS) 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 interval from best response to progression or death from any cause. Bone

marrow aspirates were analyzed for measurable residual disease (MRD) using the EuroFlow standardized protocol (Sensitivity threshold: 10^{-5}) [6].

Adverse events (AEs) 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 June 2020 to March 2025. Four had primary PCL, 7, secondary PCL and 7 were men. Median age was 54 years (IQR, 44-61 years). Subjects were Revised International Staging System (R-ISS) stage-II or -III. Median numbers of prior therapies were 4 (IQR, 2-5). Seven subjects had a prior autologous haematopoietic cell transplant and 1, 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 5, complex cytogenetic abnormalities defined as ≥ 3 clonal abnormalities [9, 10]. (Table 1)

All subjects had CRS, including 8 (73%) grade 1 and 3 (27%) grade 2 CRS.(Table 2). Median CRS duration was 5 days (IQR, 4-5 days). Management included tocilizumab and corticosteroids. All subjects had transient increases in serum interleukin-6 and ferritin. One subjects had grade-2 ICANS. All subjects had > grade-2 haematological AEs and late immune effector cell associated haemato-toxicity (ICAHT) predominantly grades-1 to -2. [11]

All subjects responded (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 1 A). Of the 5 patients with complex karyotype, 4 obtained VGPR or better. Whereas only 1 out of 4 patients with soft tissue involvement achieved CR. Two of 3 subjects with a partial response had soft tissue involvement. All subjects had a bone marrow negative MRD-

test by day 28. The failure to attain sCR despite achieving MRD negativity might be link to extramedullary disease or specific genetic profiles (Supplementary Figure 1). Median PFS was 290 days (95% Confidence Interval [CI], 90 days, not reached but must exceed 420 days; Figure 1 B). Median survival was 320 days (120 days, not reached but must exceed 690 days; Figure 1 C). Four patients remained progression-free post-CAR T-cell therapy, and 7 patients experienced recurrence during the follow-up period. Five of 7 subjects who progressed received a 2nd CAR T-cell infusion all of whom achieved a ≥ partial response, of whom, 3 patients survived over 600 days. (Table S1). Our study advances beyond comparative analyses of anti-BCMA CAR-T 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 (GVHD) after an allotransplant (n=1), and hemorrhage (n=1; Patient 6 died from massive hemoptysis [pulmonary hemorrhage] secondary to severe, grade 4 thrombocytopenia at 4 months post-infusion).

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 7 individuals achieving a CR, underscoring the substantial antitumor activity of CAR T cells in this aggressive hematologic malignancy. Notably, among those who experienced disease relapse, 5 patients 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 PFS of 345 days, compared to 120 days for those with secondary PCL. Similarly, median survival was 375 days for primary PCL and 300 days for secondary PCL (Supplementary Figure 2). 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 more precisely delineate treatment efficacy and prognostic determinants.

Our data suggest CAR T-cell are a potential therapy of 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 patient characteristics, and prior treatment histories introduces potential confounding 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.

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Table 1. Baseline characteristics of the PCL patients

Characteristic	Total (N=11)
Median age, years（IQR）	54(44-61)
PCL type, No. (%)	
pPCL	4(36%)
sPCL	7(64%)
Sex, No. (%)	
Female	4(36%)
Male	7(64%)
Type of myeloma, No. (%)	
IgG-κ	4(36%)
IgA-λ	2(18%)
Light chain	1(9%)
IgD-λ	3(27%)
Nonsecretory	1(9%)
R-ISS disease stage, No. (%)	
II	4(36%)
III	7(64%)
Karnofsky Performance score, No. (%)[a]	
50-60	2(18%)
70-80	8(73%)
90-100	1(9%)
High tumor burden, No. (%)[b]	7(64%)
Soft tissue involvement, No. (%)	4(36%)
Complex chromosomal karyotypes, No.(%)	5(45%)
Renal impairment, No.(%)	2(18%)

Previous therapy lines, median (IQR)	4(2-5)
⩾3, No. (%)	7(64%)
Previous therapies	
Proteasome inhibitors, No. (%)	
Bortezomib	11(100%)
Ixazomib	2(18%)
Carfilzomib	5(45%)
Immunomodulatory drugs, No. (%)	
Lenalidomide	11(100%)
Pomalidomide	7(64%)
Anti-CD38 monoclonal antibodies, No. (%)	7(64%)
Previous ASCT, No. (%)	7(64%)
Previous allo-HSCT, No. (%)	1(9%)
Other	
Selinexor, No. (%)	4(36%)
Venetoclax, No. (%)	1(9%)

1. Abbreviations: ASCT, autologous stem-cell transplantation; allo-HSCT, allogeneic hematopoietic stem cell transplantation; Ig, immunoglobulin; R-ISS, Revised International Staging System; pPCL, primary plasma cell leukemia; sPCL, secondary plasma cell leukemia.
2. Baseline assessments were performed prior to lymphodepleting chemotherapy.
3. 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.

Table 2. Adverse Events

Patient no.	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
Hematological											
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
Hypofibrinogenaemia	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

Abbreviation: ICAHT, immune effector cell associated hematotoxicity; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; COVID-19, Corona Virus Disease 2019; APTT, activated partial thromboplastin time; AST,aspartate aminotransferase;ALT, alanine aminotransferase.

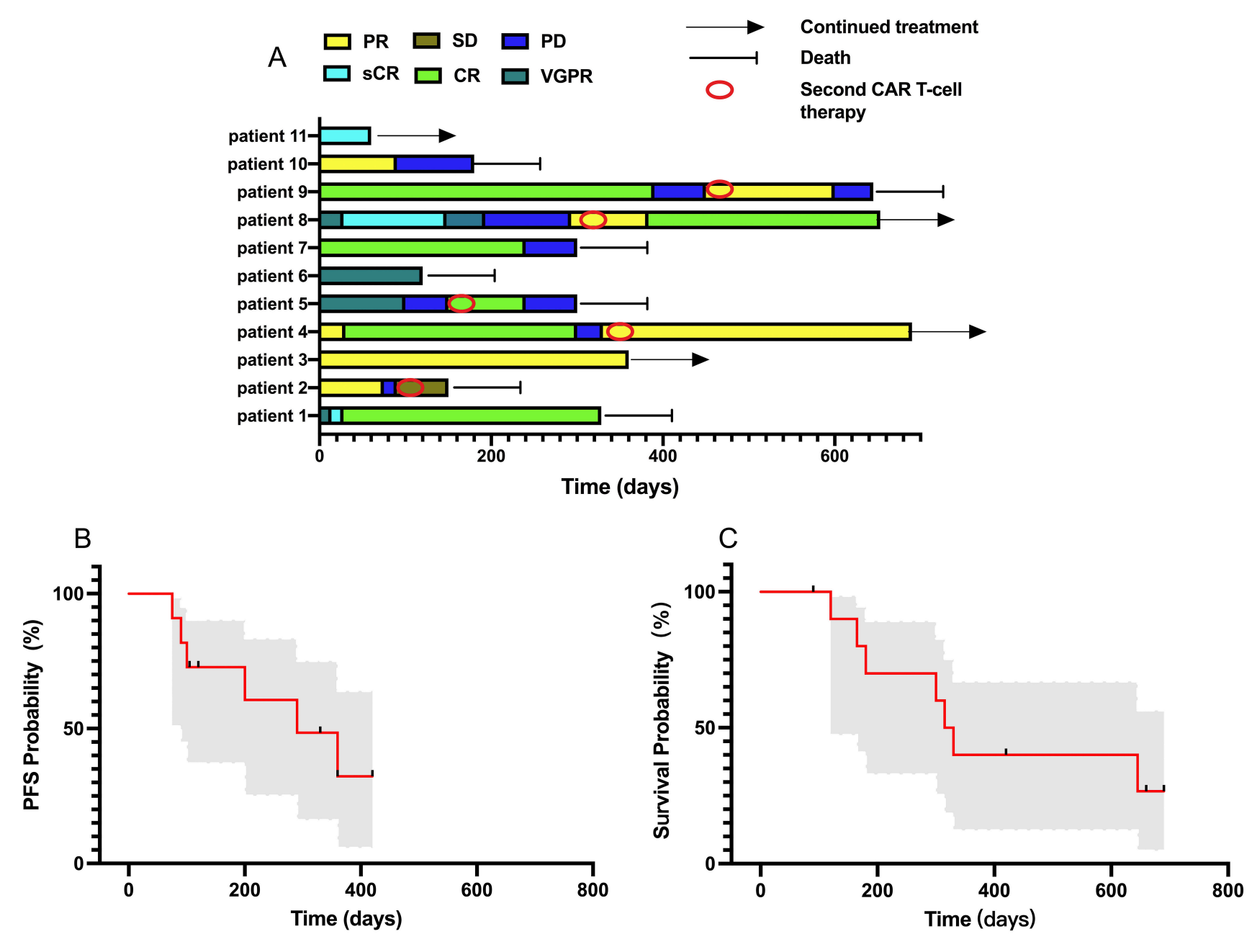
*Patients who, after relapsing following initial CAR T-cell therapy, received a second infusion of CAR T cells targeting a different antigen.

[a]CRS and ICANS were graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) consensus criteria. The numbers 1-4 indicate the severity grade. Hematological toxicity were graded according to CTCAE v5.0.

[b]Hypogammaglobulinemia was defined as an IgG level < 400 mg/dL.

Figure 1. Clinical outcomes of patients with plasma cell leukemia treated with CAR T-cell therapy.

(A) Responses. Treatment duration following the first CAR T-cell therapy. Each bar represents one subject in this study. (B-C) Kaplan–Meier estimates of PFS (B) and survival (C) . Estimated survival probability; Shaded area 95% confidence interval. pPCL, primary plasma cell leukemia; sPCL, secondary plasma cell leukemia; CAR, chimeric antigen receptor; sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response; SD, stable disease; PD, progressive disease.NE, not estimated.

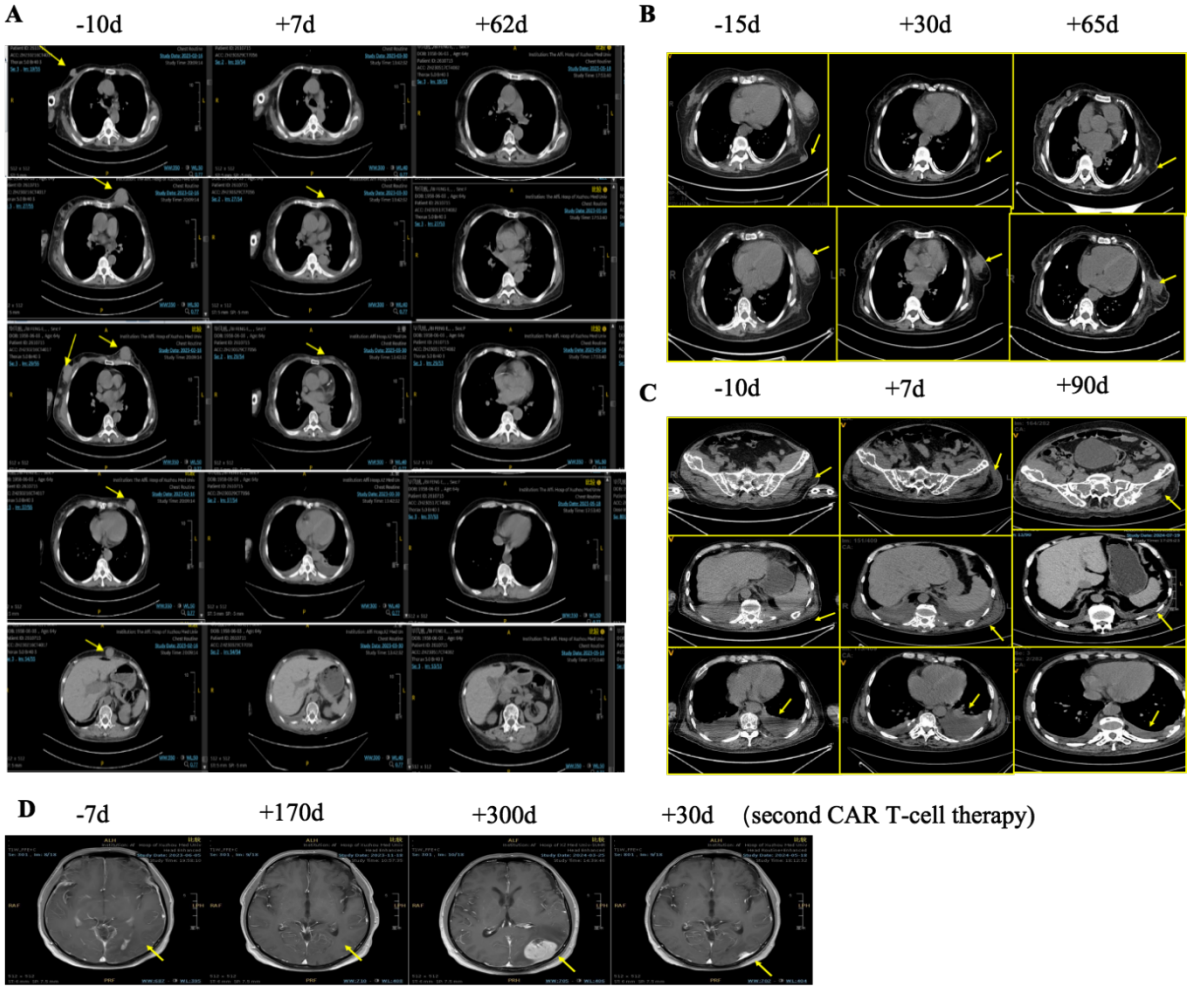

A
PR
SD
PD
sCR
CR
VGPR
Continued treatment
Death
Second CAR T-cell therapy
patient 11
patient 10
patient 9
patient 8
patient 7
patient 6
patient 5
patient 4
patient 3
patient 2
patient 1
0
200
400
600
Time (days)
B
PFS Probability (%)
100
50
0
0
200
400
600
800
Time (days)
C
Survival Probability (%)
100
50
0
0
200
400
600
800
Time (days)

Supplementary information

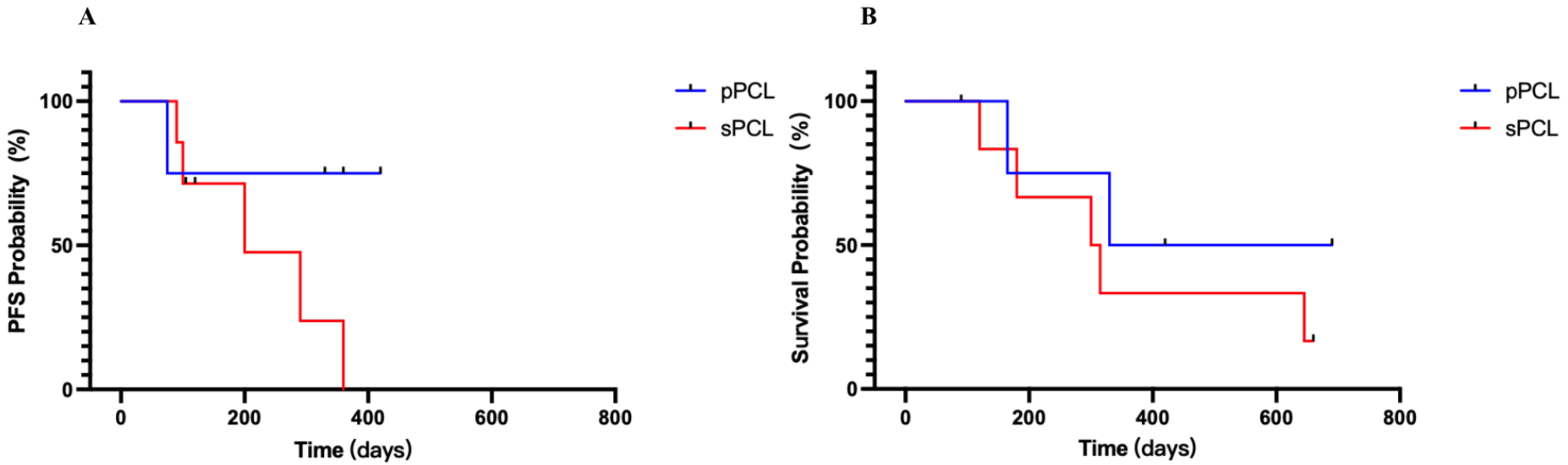
Online Supplementary Table S1. Patients and treatment character.

Patient no./ Gender/Age	PCL type	Types Serum Protein Electrophoresis	Type of CAR T-cell	CAR T-cell dose (10^6/kg)	Response (Day 28)	Best response	Months until relapse/progression after CAR T	Subsequent follow up (months after CAR T)	Second relapse (best response, months)	Survival (months from first CAR T)
1/M/41	pPCL	λ Light chain	BCMA	2	sCR, MRD Neg	sCR	No	Allo-HSCT (4)	No	11
2/F/62*	pPCL	Nonsecretory	GPRC5D	2	PR, MRD Neg	PR	2.5	BCMA-C (2.6)	Yes (PR, 2)	5.5
3/F/70	pPCL	IgG-κ	BCMA	1.6	PR, MRD Neg	PR	No	ND	No (PR,14 +)	14 +
4/M/57*	pPCL	IgD-λ	GPRC5D	4	PR, MRD Neg	CR	10	BCMA-C (11)	No (PR,12+)	23+
5/F/39	sPCL	IgG-κ	BCMA	1.5	VGPR, MRD Neg	VGPR	3.5	GPRC5D-C (5)	Yes (CR, 3)	10
6/M/54	sPCL	IgA-λ	BCMA	1.5	CR, MRD Neg	CR	No	ND	No	4
7/M/51	sPCL	IgG-κ	BCMA	2	VGPR, MRD Neg	CR	10	ND	No	10.5
8/M/61	sPCL	IgD-λ	GPRC5D	2	VGPR, MRD Neg	sCR	6	BCMA-C (10)	No (sCR,12 +)	22 +
9/F/61*	sPCL	IgD-λ	BCMA	0.5	CR, MRD Neg	CR	12	GPRC5D-C (14)	Yes (PR, 5.5)	21.5
10/M/57*	sPCL	IgG-κ	GPRC5D	2	PR, MRD Neg	PR	3	ND	No	6
11/M/41	sPCL	IgA-λ	GPRC5D	4	sCR, MRD Neg	sCR	No	ND	No	3+

M, male; F, female; pPCL, primary plasma cell leukemia; sPCL, secondary plasma cell leukemia; CAR, chimeric antigen receptor; Allo-HSCT, allogeneic hematopoietic stem cell transplantation; BCMA-C, B-cell maturation antigen CAR T-cell; GPRC5D-C, G protein-coupled receptor, class C group 5 member D-CAR T-cell; sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response; MRD, minimal residual disease; ND, not done; +, still alive ; *, Patients with soft tissue involvement.



Online Supplementary Figure 1. Imaging findings of extramedullary involvement before and after CAR T-cell therapy . (A-C) Chest CT images from Patient 2, 9, and 10 demonstrate representative extramedullary lesions (yellow arrows). (D) Brain MRI image from Patient 4 shows a solitary metastatic lesion (yellow arrow). CAR, chimeric antigen receptor.



Supplementary Figure 2. Kaplan-Meier curves depicting outcomes based on disease subtype. (A) Progression-free survival (PFS) and (B) Survival for patients with primary plasma cell leukemia (pPCL) versus secondary plasma cell leukemia (sPCL).