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Five-year survival and infectious complications of donor-derived CD7 CAR-T therapy in T-ALL

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Running title: Five-year outcomes of donor-derived CD7 CAR-T therapy

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Data-sharing statement

Correspondence for material requests should be addressed to the corresponding author. All data associated with this study are present in the paper or the Supplementary Materials.

Clinical trial registration: ChiCTR2000034762

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Competing interests

Authors declare that they have no competing interests.

Contributions

LS, XF and JP contributed to study design, data interpretation and manuscript writing. LS, XF, JP, TL, YW, CZ and ZW contributed to data generation and analysis. JP and ZL contributed to patient treatments. XF and JP directed the study and had final responsibility to submit for publication.

CD7-directed chimeric antigen receptor (CAR)-T cell therapy has shown efficacy in relapsed or refractory T-cell acute lymphoblastic leukemia (r/r T-ALL), but sustained targeting of CD7 may compromise normal T-cell immunity.¹⁻⁴ We previously reported the initial and two-year outcomes of a phase I trial of donor-derived CD7 CAR-T cells, showing high response rates but risk of relapse and severe infections.^{5,6} Whether extended follow-up tips the scale toward either relapse or treatment-related morbidity, however, has not been adequately quantified. Here, we report the five-year outcomes of this trial.

Twenty patients with r/r T-ALL were enrolled between July and December, 2020. With a data cutoff of December 20, 2025, the median follow-up duration was 62.9 months (range, 60.6-65.9). Six patients remained under this follow-up beyond the previous cutoff (December 20, 2022): three (E003, E008, and E018) received CD7 CAR-T cells manufactured from their prior stem cell transplantation (SCT) donors without post-CAR SCT consolidation, whereas three (E005, E015, and E019) received CAR-T cells from new donors followed by SCT consolidation. The study was approved by Beijing Boren Hospital Institutional Review Board. Baseline characteristics, early efficacy and safety were previously reported.^{5,6}

Among the three patients followed long-term without SCT consolidation, late grade ≥ 3 cytopenias occurred in E008 and E018 and persisted until death, except for transient neutropenia in E018. Two patients newly developed graft-versus-host disease (GVHD) in this follow-up: E003 developed grade 1 skin GVHD at month 52.5, which was controlled with corticosteroids, and E008 developed grade 2 liver GVHD at month 31.0, possibly related to cryopreserved donor peripheral blood stem cell (PBSC) infusion, which persisted until death at month 32.1 (Figure 1A; Supplementary Table S1). No subsequent malignant neoplasms were observed.

Three severe infections ($\geq$ grade 3) were newly documented (Figure 1A; Supplementary Table S1). E008 developed grade 3 *Klebsiella pneumoniae* pneumonia complicated with grade 3 CMV/EBV infections at month 27.4, progressing to grade 5 at month 32.1. E018 had intermittent SARS-CoV-2

positivity at month 38.0, then grade 3 *Paeruginosa* pneumonia with grade 3 CMV/bacterial co-infections at month 50.0, later developed Aspergillus sinusitis and died of fungal encephalitis at month 56.0. E003, with prior grade 3 CMV encephalitis (months 11.0-13.3), had grade 1 COVID-19 infection at month 29.0 and grade 3 *Pneumocystis jirovecii* pneumonia at month 52.0, which resolved with treatments. Longitudinal CMV/EBV DNA copy number in these three patients are shown in Supplementary Figure S1A.

In the whole cohort, eight (67%) of 12 patients without SCT consolidation developed infections of any grade, including one (8%) each with grade 1 and grade 3-4 and six (50%) with grade 5 (Figure 1A). Grade ≥ 3 infections occurred in two (50%) of four patients receiving the low dose and five (63%) of eight receiving the target dose, with grade 5 infections occurred in one (25%) of four and five (63%) of eight, respectively; neither the overall infection rate nor the grade 5 infection rate differed significantly by dose (Supplementary Figure S1B). Grade 5 infections occurred in four (80%) of five patients with early GVHD (≤ 1 month post-CAR) versus two (28%) of seven without early GVHD, suggesting a potential association between early GVHD and lethal infections; no obvious association was observed for late or any-time GVHD (Supplementary Figure S1C). Among the seven patients with SCT consolidation, one died of previously reported engraftment syndrome.⁶

Of the six patients followed for survival and disease status, two of three without SCT consolidation (E008 and E018) died of infections, while E003 remained in remission until the data cutoff (65.4 months). All three with SCT consolidation maintained disease-free survival for a median duration of 61.2 months (range, 60.6-64.6). Outcomes after relapse were poor. Among the six relapsed patients, four received subsequent donor-derived CD5 (n=3) or CD7 (n=1) CAR-T therapy and two received chemotherapy. Five died of infections and one of disease progression (Figure 1A). The four patients with CD7-negative relapse had short survival after relapse (range, 4.1-10.9), with overall survival (OS) after CD7 CAR-T cell infusion ranging from 8.8-18.2 months. In contrast, the two with CD7-positive relapse achieved prolonged survival after relapse (9.8 and 25.9 months) and OS after

CD7 CAR-T cell infusion (20.8 and 34.97 months) (Supplementary Figure S2A).

In the whole cohort, the cumulative incidences of non-relapse mortality (NRM) and relapse were 35% and 30%, respectively (Figure 1B). Competing-risk analyses suggested a higher relapse incidence in the new-donor cohort but higher NRM in the prior-SCT cohort; however, no formal statistical comparisons were performed between groups (Figure 1C-D). Relapse occurred predominantly within the first year after CAR-T therapy, whereas NRM continued to accrue over time (Figure 1E).

The 5-year OS rate for all 20 patients was 24.1% (95% confidence interval [CI], 3.6-44.7), with a median OS of 18.2 months (95% CI, 12.5-55.0) (Figure 2A). Among 19 responders, the median progression-free survival (PFS) and duration of response (DOR) were 11.0 months (95% CI, 6.9-55.0) and 10.5 months (95% CI, 6.4-54.5), respectively. The 5-year PFS and DOR rates were both 24.5% (95% CI, 3.9-45.2) (Figure 2B-C). In an exploratory post-hoc analysis, 5-year OS, PFS, and DOR were each 10.6% among patients without SCT consolidation, compared with 42.9% among those who underwent SCT (Figure 2D-F). The 5-year OS and PFS rates were both 50.0% (95% CI, 18.8-100) in the low-dose group (n=4) and 21.5% (95% CI, 7.9-58.6) in the target-dose group (n=16 and n=15 for OS and PFS, respectively; Supplementary Figure S2B).

Among the three patients without SCT consolidation followed, CAR-T cells reappeared by flow cytometry in E018 between months 33.4 and 49.1, while CAR transgenes remained detectable at the last assessment, suggesting that the late resurgence may have reflected re-expansion or redistribution of residual CAR-T cells. E008, who received unmanipulated G-CSF mobilized PBSCs at month 30.9, had lost CAR-T cells at month 14.1 but retained transgenes at the last assessment (month 31.5) before death. E003, who received purified donor CD34⁺ stem cells plus unmanipulated G-CSF mobilized PBSCs at month 16.0, lost CAR-T cells at month 22.7 and transgenes at month 29.3 (Figure 3A-B). Given the different cellular products, limited patient number and unavailable PBSC composition, the effect of these infusions on CAR-T cell kinetics cannot be determined.

Total T-cell recovery remained incomplete. E018 showed a late decline at months 42.6-54.7 after

initial normalization; E003 developed secondary T-cell deficiency at month 6 but recovered to the normal range by month 21.3; E008 had persistently subnormal levels. CD7⁺ T cells re-emerged but remained below the normal range in E003 and E018 (Figure 3C). In E003, CD7⁺ T cells reappeared at month 25.6, as previously reported.⁶ In E018, CD7⁺ T cells became detectable between months 42.6 and 50.2 and then became undetectable again. During this period, CAR-T cells remained detectable by flow cytometry but later became undetectable, whereas CAR transgenes remained detectable with a modest increase. Neither peripheral blood nor bone marrow morphology showed evidence of leukemia relapse, and MRD assessments remained negative, suggesting that the transiently detectable CD7⁺ T cells were more likely nonmalignant T cells than relapsed leukemia. The temporal overlap between CD7⁺ T-cell re-emergence and detectable CAR-T cells, followed by loss of both populations, raised the possibility of ongoing on-target interactions between residual CAR-T cells and CD7⁺ T cells. Sustained CD4⁺ T-cell counts above 500 cells/ μ L were observed only in E003, and the CD4⁺/CD8⁺ T-cell ratio recovered to the reference range in two of the three patients (Figure 3C).

NK-cell counts normalized by month 2 and remained normal in E008, declined below the normal range at month 25.6 but recovered by month 52.0 in E003, and remained below the normal range in E018. B-cell counts remained below the normal range in E003 and E008, whereas recovery was observed in E003 at month 52.0 (Figure 3C). In the whole cohort, among seven patients with severe infections, most had T-cell deficiency (86%, 6/7), while NK-cell deficiency was similar between severe (71%, 5/7) and non-severe (60%, 3/5) infection groups (Figure 3D). Although descriptive, these findings suggest that persistent T-cell abnormalities may be more relevant than NK-cell deficiency to long-term infectious vulnerability, warranting validation in larger cohorts.

With few reports addressing the long-term safety and efficacy of CD7 CAR-T therapy to date, this five-year update revealed a shift in the major risks over time. Relapse occurred predominantly within the first year, whereas infection-related NRM persisted throughout the five-year follow-up. Among patients without SCT consolidation, late-onset severe infections were accompanied by incomplete T-

cell recovery, with CD7⁺ T-cell counts remaining below the normal range in all three patients followed long-term. Persistent CAR activity may impair normal CD7⁺ T-cell recovery and increase infection risk, although these associations remain descriptive.

With four patients remaining in remission beyond five years, long-term outcomes appeared more favorable after SCT consolidation, consistent with other reports suggesting a benefit of SCT,^{7,8} although the small, non-randomized groups preclude definitive conclusion. In addition, limited specimen availability prevented detailed long-term immune profiling of CAR-T and non-CAR T cells. Nonetheless, these findings support the potential for durable remission after donor-derived CD7 CAR-T therapy, particularly with SCT consolidation, while highlighting late infection-related mortality and incomplete immune reconstitution as important barriers to long-term benefit.

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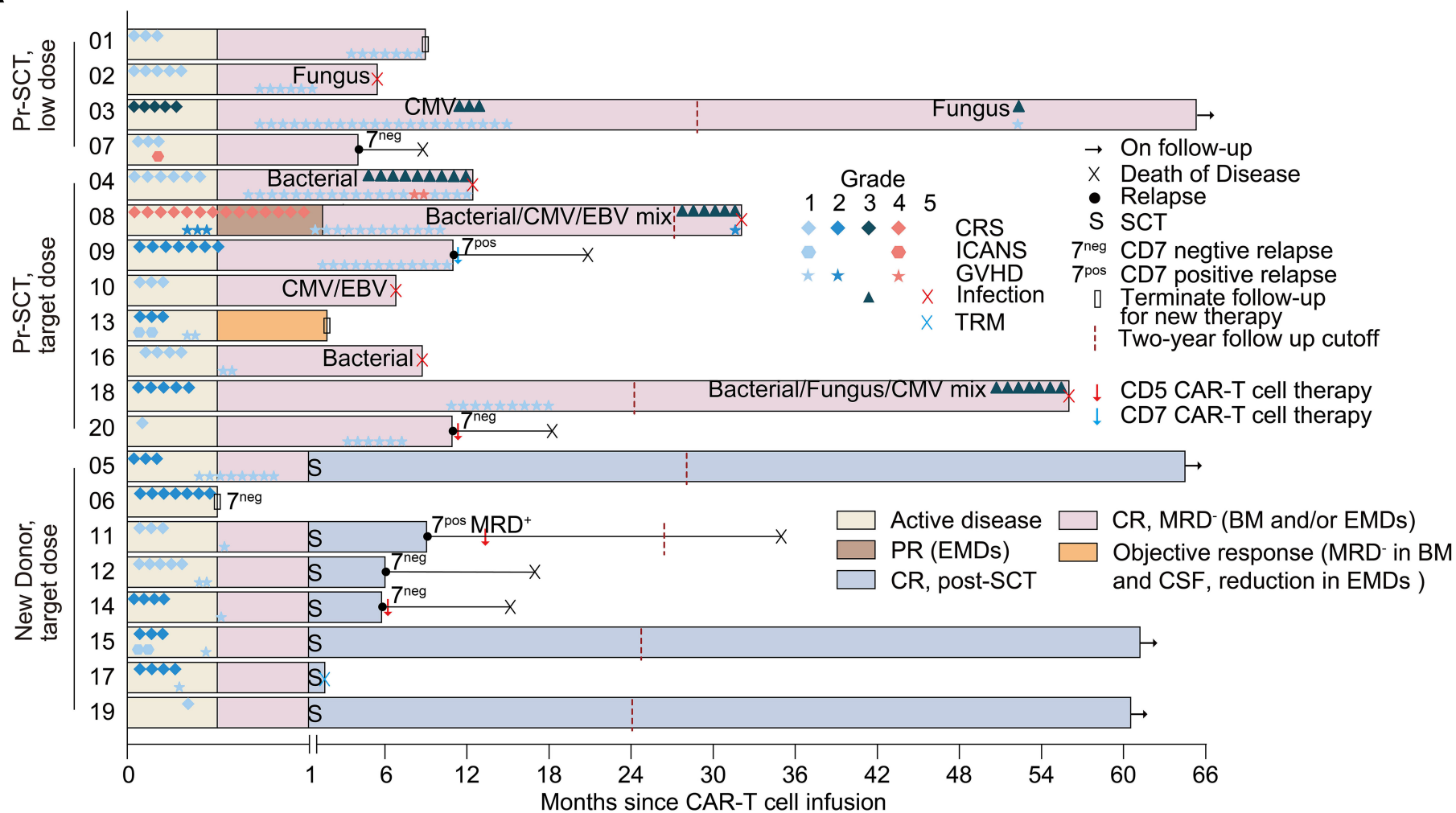
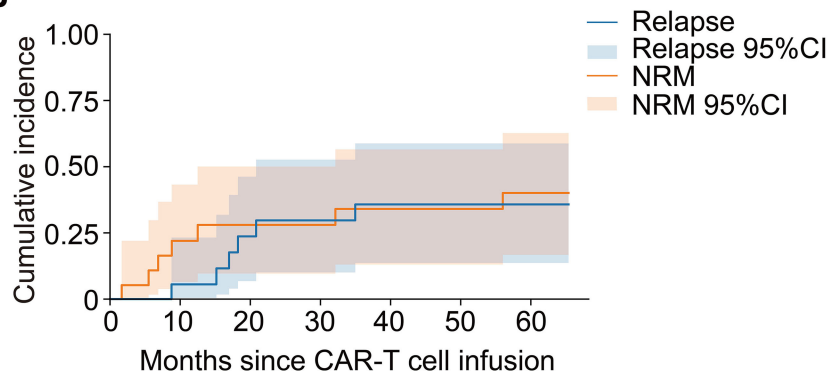
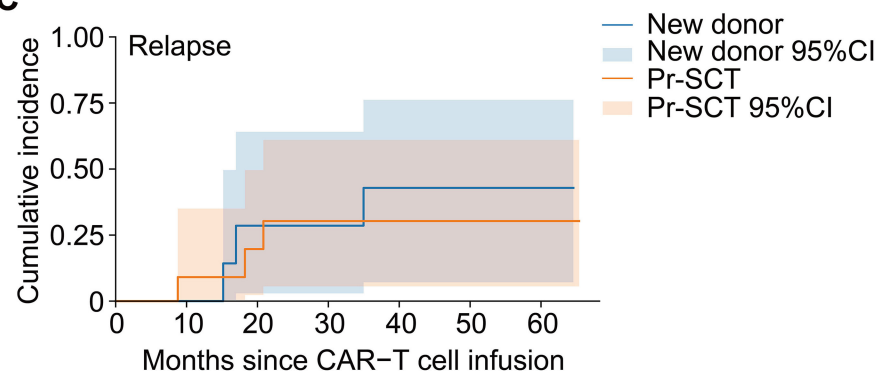
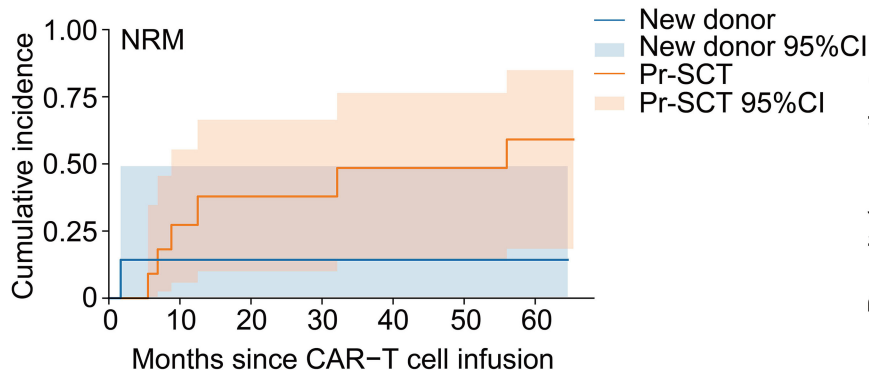
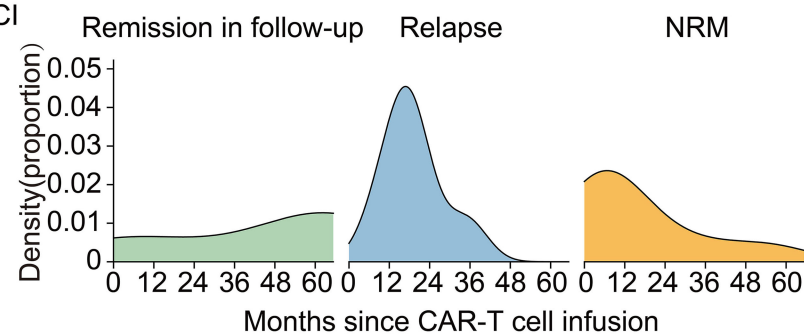
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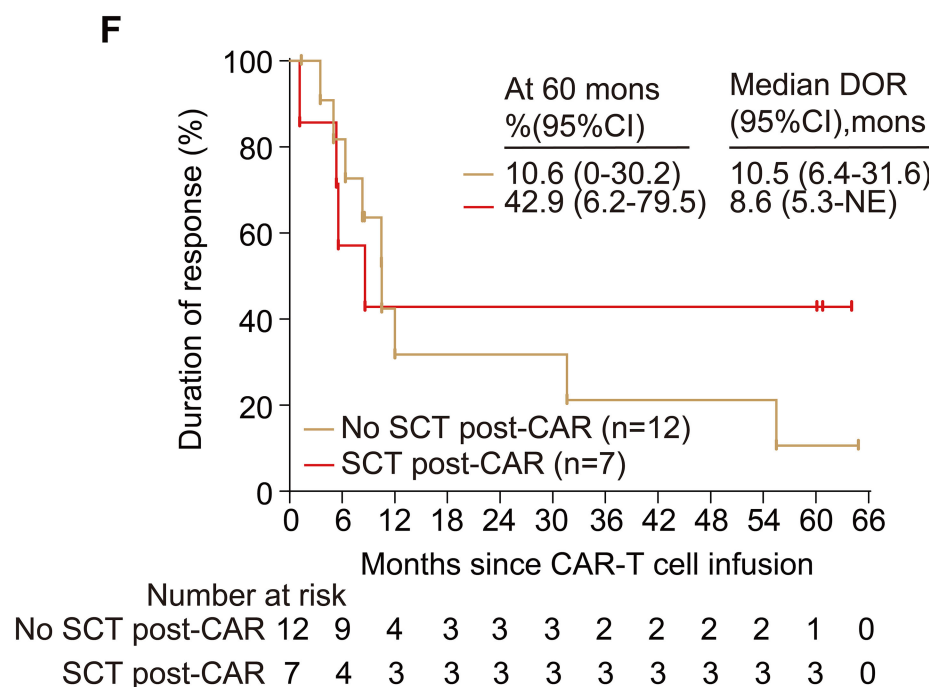
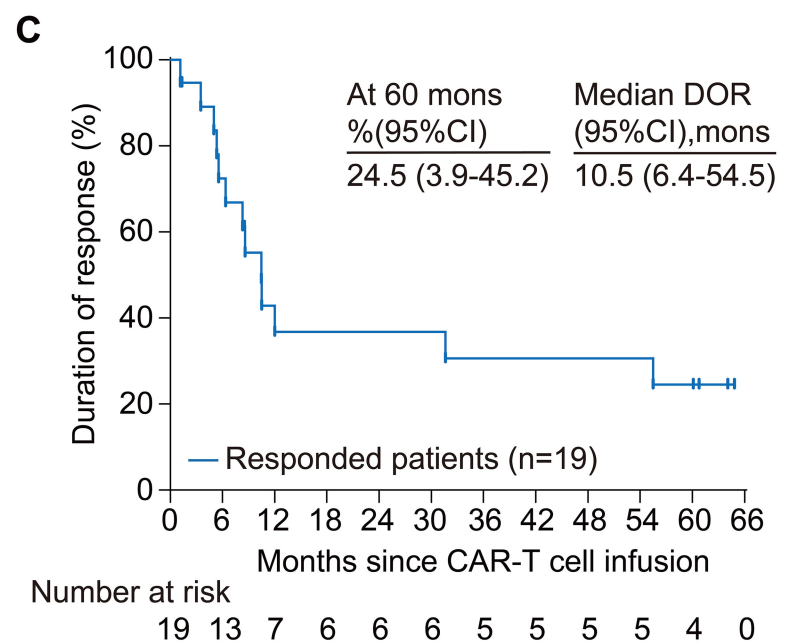
Figure 1. Adverse event and clinical response. (A) Swimmer plot detailing the timeline of clinical responses, adverse events (AEs), and overall outcomes for individual patients (n=20) following CAR-T cell infusion. Background colors of the bars represent the patient's disease status. Superimposed symbols denote the occurrence and timing of specific AEs. For infections, only grade ≥ 3 events are shown. (B) Overall cumulative incidence of relapse (blue line) and non-relapse mortality (orange line) following CAR-T cell infusion. (C) Cumulative incidence of relapse stratified by cohort. (D) Cumulative incidence of NRM stratified by cohort. Shaded regions represent the corresponding 95% CI. (E) Density plots illustrating the proportional distribution of clinical status, including remission in follow-up (green), relapse (blue), and NRM (orange). CI, confidence interval; NRM, non-relapse mortality; Pr-SCT, prior stem cell transplantation. CAR, chimeric antigen receptor; SCT, stem cell transplantation; CR, complete remission; MRD, minimal residual disease; BM, bone marrow; EMDs, extramedullary diseases; PR, partial remission; CSF, cerebrospinal fluid; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; GVHD, graft-versus-host disease; TRM, transplantation-related mortality.

Figure 2. Kaplan-Meier estimates of survival. (A) OS for all patients (n=20) following CAR-T cell infusion. (B) PFS for patients who achieved a response (n=19). (C) DOR for responding patients (n=19). (D-F) OS (D), PFS (E), and DOR (F) comparing patients who did not receive SCT consolidation after CAR-T cell therapy versus those who did. Vertical tick marks represent censored observations. CI, confidence interval; DOR, duration of response; NE, not estimable; OS, overall survival; PFS, progression-free survival; SCT, stem cell transplantation.

Figure 3. CAR-T cell pharmacokinetics and lymphocyte subsets. (A) Kinetics of CAR-T cells in peripheral blood after infusion. (B) CAR transgene copy numbers per μg of genomic DNA in

peripheral blood. (C) Kinetics of peripheral blood lymphocyte subsets, including CD7⁺ T cells, CD7⁻ T cells, CD4⁺ T cells, CD8⁺ T cells, total T, NK, B cells and CD4⁺/CD8⁺ T-cell ratio. The lower reference limits for total B cell, T cell and NK cell in healthy individuals apply to people aged 18 and older. (D) Stacked bar charts showing the association of T cell recovery (left) and NK cell recovery (right) according to severity of late-onset infections.

A**B****C****D****E**



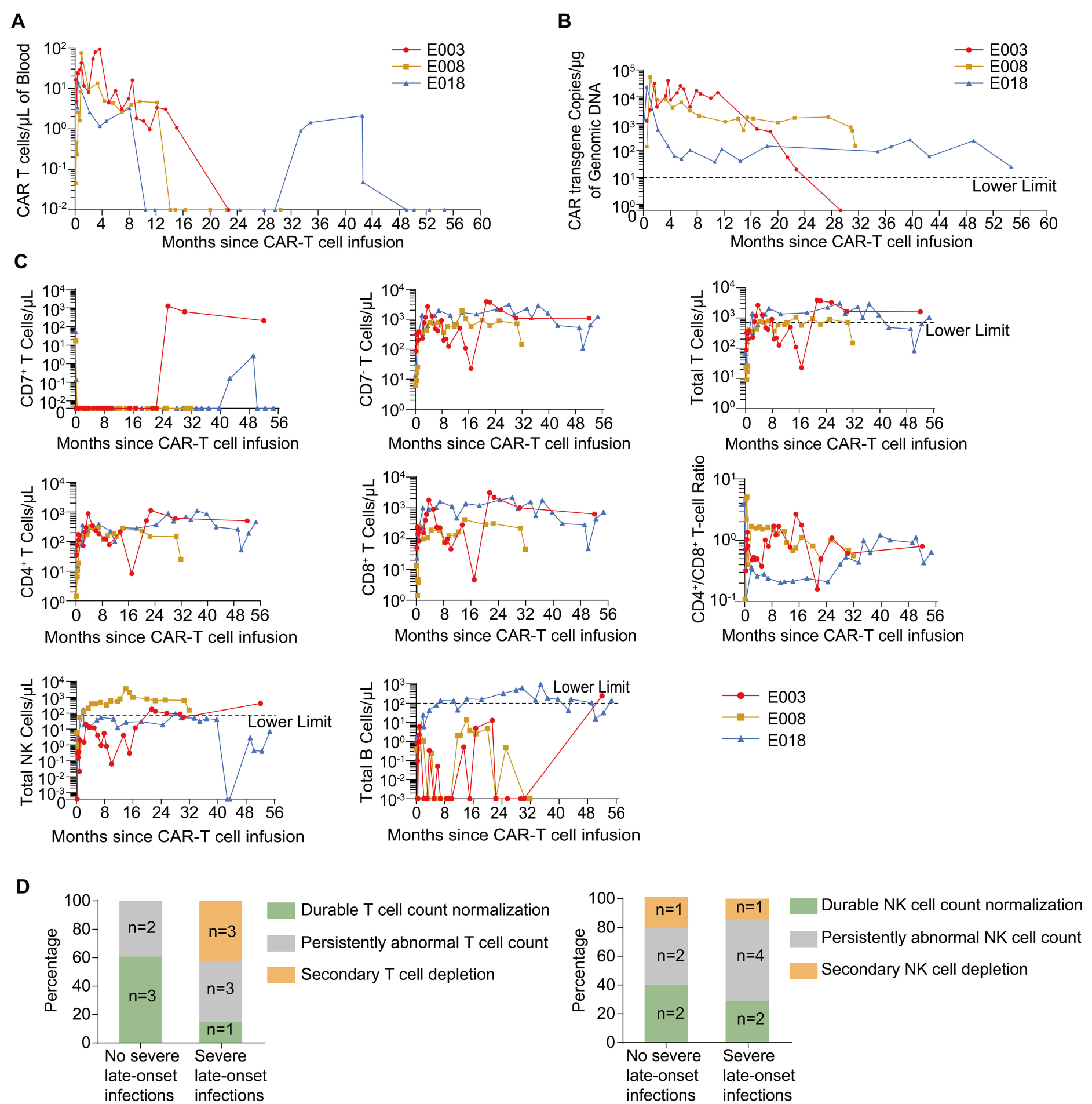


Table S1. Adverse events, response and outcomes of individual patients

Cohort	Patient (no.)	CRS (G)	ICANS (G)	GVHD (G)	Infection (G)	Response at day 30	SCT-Post CAR/Day	Relapse time/FU time (mons)/outcome
Prior-SCT Donor, 5×10⁵ (±30%)/kg	E001	1	0	1	1	CR	No	-/9.0/Loss FU
	E002	1	0	1	5	CR	No	-/5.5/D (Fungus)
	E003	3	0	1	3	CR	No	-/65.4/CCR
	E007	1	4	0	0	CR	No	4.1/8.8/D
Prior-SCT Donor, 1×10⁶ (±30%)/kg	E004	1	0	4	5	CR	No	-/12.5/D (Bac)
	E008	4	0	2	5	PR	No	-/32.1/D (Bac)
	E009	2	0	1	0	CR	No	11.0/20.8/D
	E010	1	0	0	5	CR	No	-/6.8/D (Virus)
	E013	2	1	1	0	Resp*	No	-/1.8/Loss FU
	E016	1	0	1	5	CR	No	-/8.7/D (Bac)
	E018	2	0	1	5	CR	No	-/56.0/D (Fungus)
	E020	1	0	1	0	CR	No	10.9/18.3/D
New Donor, 1×10⁶ (±30%)/kg	E005	2	0	1	0	CR	Yes/32	-/64.6/CCR
	E006	2	0	0	0	NR	No	-/0.5/Loss FU
	E011	1	0	1	0	CR	Yes/31	9.1/26.4/D
	E012	1	0	1	0	CR	Yes/32	6.0/17.0/D
	E014	2	0	1	0	CR	Yes/33	5.8/14.9/D
	E015	2	1	1	0	CR	Yes/30	-/61.3/CCR
	E017	2	0	1	0	CR	Yes/37	-/1.7/D (ES)
	E019	1	0	0	0	CR	Yes/31	-/60.6/CCR

*Achieve objective response (MRD⁻ in BM and CSF, and reduction in EMDs) until out of trial.

“–” indicates no relapse during follow-up.

Abbreviations: no., number; SCT, stem cell transplantation; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; GVHD, graft-versus-host disease; G, grade; mons, months; CNS, central nervous system; CR, complete remission; NR, non-response; CCR, continuous complete remission; D, death; ES, engraftment syndrome; FU, follow-up; Bac, bacterial.

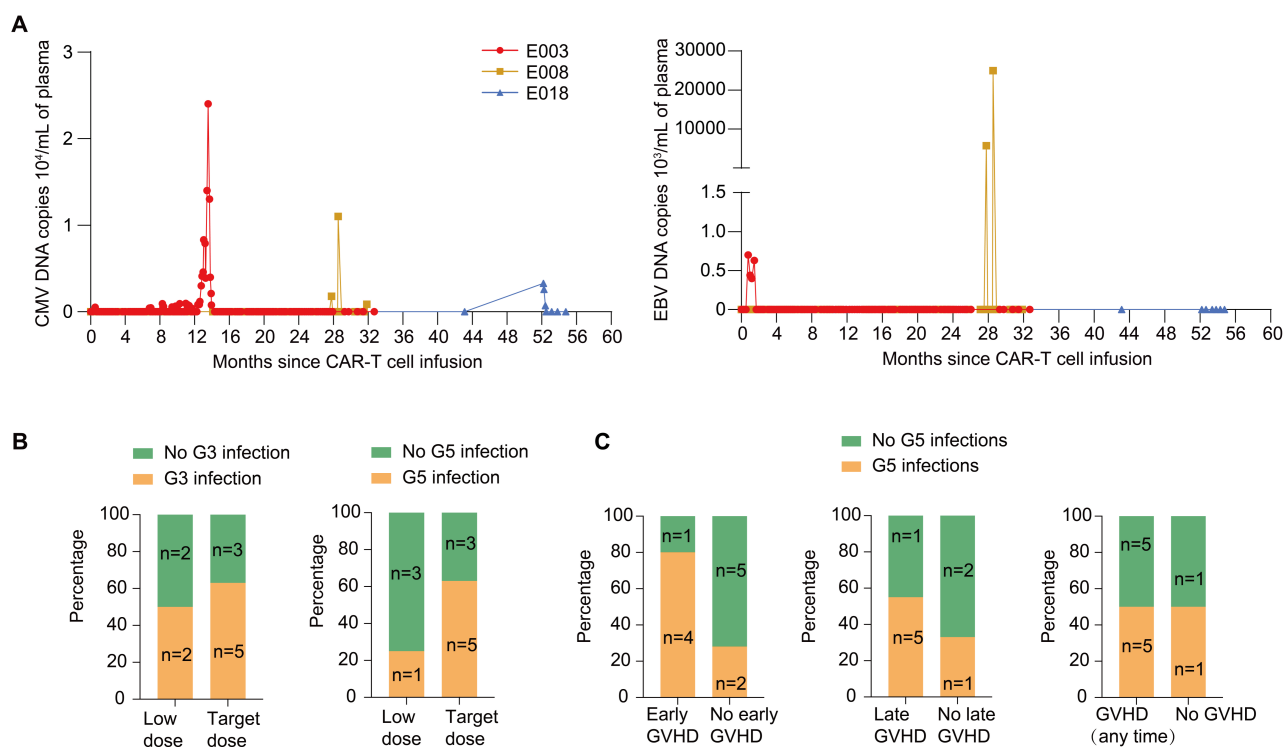


Figure S1. Long-term viral monitoring and associations of infection with CAR-T cell dose and GVHD. (A) Copy numbers of CMV DNA and EBV DNA in plasma for individual patients (E003, E008 and E018), as determined by quantitative polymerase chain reaction. (B) Stacked bar plots showing the proportions of patients with and without grade ≥ 3 or grade 5 infections according to CAR-T cell infusion dose. (C) Stacked bar plots showing the proportions of patients with and without grade 5 infections according to the occurrence of early GVHD (within 30 days after CAR-T cell infusion), late GVHD (>30 days after infusion), or GVHD at any time during follow-up. Numbers within the bars indicate the number of patients in each category. Analyses included the 12 patients who did not undergo subsequent SCT.

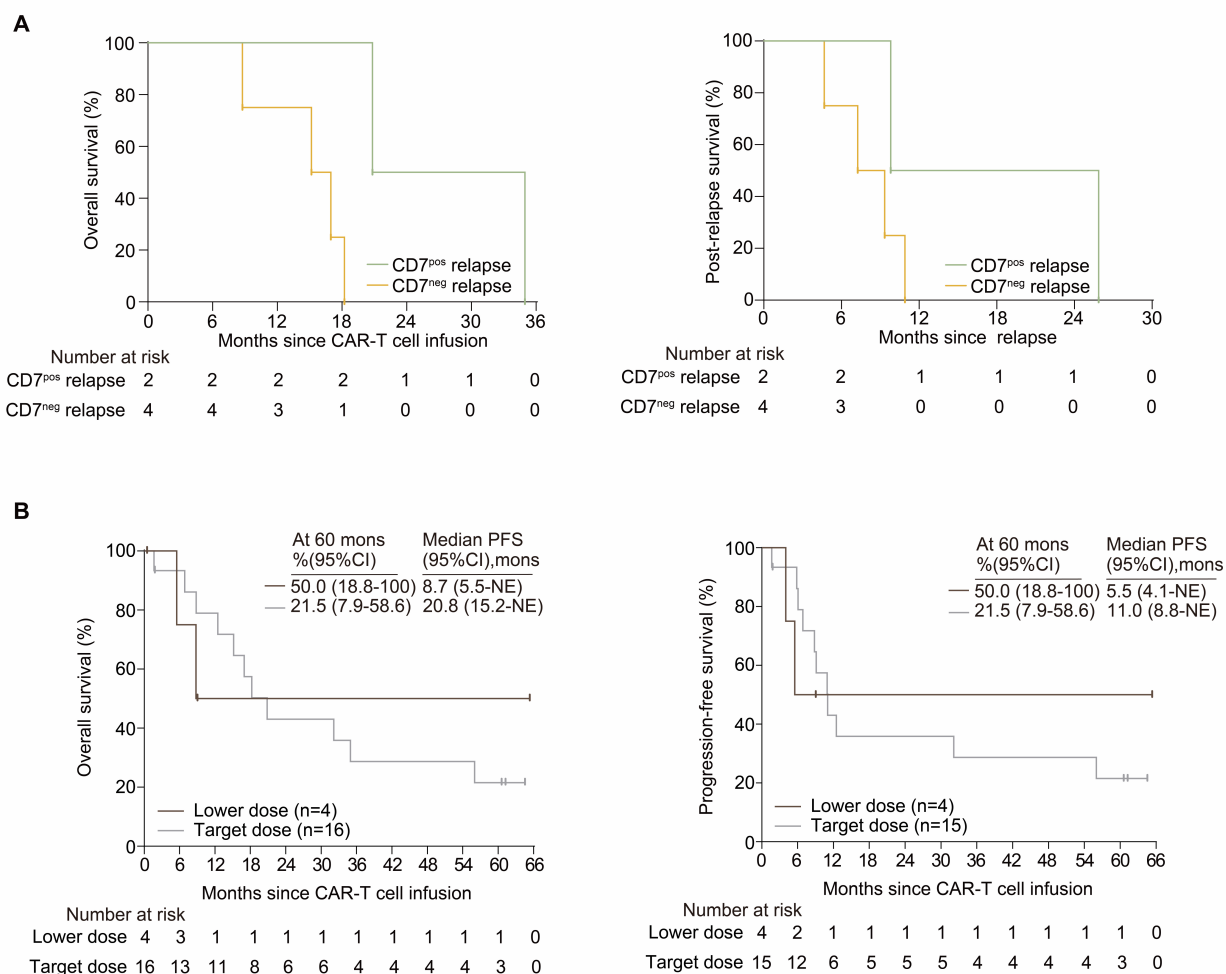


Figure S2. Kaplan-Meier estimates of survival and clinical response. (A) OS and post-relapse survival for relapsed patients (n=6) following CAR-T cell infusion, stratified by CD7-positive (n=2) and CD7-negative (n=4) relapse. (B) OS and PFS according to CAR-T-cell dose level (lower dose vs target dose).