Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Long-term Outcomes and Immune Reconstitution after Tisagenlecleucel in Relapsed or Refractory Large B-cell Lymphoma: A Single-institution Retrospective Study in Japan with Over 3 years Follow-up

Futoshi Yoshino

fuyoshin@ncc.go.jp

National Cancer Center Hospital: Kokuritsu Gan Kenkyu Center Chuo Byoin https://orcid.org/0009-0008-2817-3102

Shinichi Makita

National Cancer Center Hospital: Kokuritsu Gan Kenkyu Center Chuo Byoin https://orcid.org/0000-0001-6609-8088

Akiko Miyagi Maeshima

National Cancer Center Hospital: Kokuritsu Gan Kenkyu Center Chuo Byoin

Wataru Takeda

National Cancer Center Hospital: Kokuritsu Gan Kenkyu Center Chuo Byoin

Tetsuro Ochi

National Cancer Center Hospital: Kokuritsu Gan Kenkyu Center Chuo Byoin

Noriko Iwaki

National Cancer Center Hospital: Kokuritsu Gan Kenkyu Center Chuo Byoin

Suguru Fukuhara

National Cancer Center Hospital: Kokuritsu Gan Kenkyu Center Chuo Byoin

Wataru Munakata

National Cancer Center Hospital: Kokuritsu Gan Kenkyu Center Chuo Byoin

Koji Izutsu

National Cancer Center Hospital: Kokuritsu Gan Kenkyu Center Chuo Byoin

---

Research Article

Keywords: CAR-T cell therapy, Tisagenlecleucel, large B-cell lymphoma, long-term outcome, immune reconstitution, hypogammaglobulinemia

Posted Date: March 19th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9115915/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Abstract

Background

Tisagenlecleucel (tisa-cel) is a CD19 chimeric antigen receptor (CAR) T-cell therapy approved for relapsed or refractory (r/r) large B-cell lymphoma (LBCL). However, real-world long-term outcomes in Japanese populations remain limited.

Methods

We retrospectively analyzed patients with LBCL who underwent leukapheresis for tisa-cel between April 2020 and July 2022 at the National Cancer Center Hospital (NCCH), Tokyo. Efficacy, survival, and immune reconstitution data were collected through December 2024.

Results

Among 24 patients who underwent leukapheresis, 21 received tisa-cel infusion. The median follow-up among survivors was 3.2 years (range, 0.2–4.3). The overall response rate (ORR) was 61.9% at 1 month and 52.4% at 3 months. The 3-year overall survival (OS) and progression-free survival (PFS) rates were 62.2% and 42.9%, respectively. $CD4^+$ T-cell depletion ($CD4^+$ T-cell < 200 cells/μL) persisted in 30.0% of complete response (CR) survivors at 1 year; however, all patients recovered at 3 years. In contrast, $CD19^+$ B-cell reconstitution remained limited, with B-cell aplasia observed in 70.0% of CR survivors at 1 year and 66.7% at 3 years. In addition, hypogammaglobulinemia (IgG < 400 mg/dL) persisted in 57.1% of CR survivors at 3 years, indicating sustained impairment of humoral immunity.

Conclusions

Tisa-cel demonstrated sustained long-term efficacy in Japanese patients with LBCL in a real-world setting. However, prolonged B-cell aplasia and persistent hypogammaglobulinemia were frequently observed, highlighting the importance of long-term immune monitoring and infection prevention strategies after CAR T-cell therapy.

Introduction

Relapsed or refractory large B-cell lymphoma (r/r LBCL) remains a clinical challenge, with poor outcomes following multiple lines of chemo-immunotherapy. The advent of CD19-directed chimeric antigen receptor (CAR) T-cell therapy has revolutionized treatment by inducing deep, durable remissions in otherwise refractory disease.

Tisagenlecleucel (tisa-cel) is a 4-1BB–costimulated CAR-T product approved for DLBCL by U.S. Food and Drug Administration (FDA) in 2018. JULIET, a pivotal study for r/r LBCL, reported an overall response rate (ORR) of 53.0%, with 39.1% of patients achieving a complete response (CR) as their best overall response [1]. In real-world settings, previous studies have reported an ORRs of 58–79% and a CR rates of 32–60% in the tisa-cel cohorts, with median overall survival (OS) ranging from 10.7 to 31 months [2–10].

In Japan, tisa-cel was approved in 2021 for patients with r/r LBCL in the third-line or later (3L+) setting. An initial multicenter real-world study reported encouraging outcomes, with an ORR of 73.0%, a 1-year OS of 67.0%, and an event-free survival (EFS) of 46.3% after a median follow-up of 6.6 months [4]. However, comprehensive long-term reports from Japan remain limited.

In this study, we conducted a single-center retrospective analysis of patients with r/r LBCL treated with commercial tisa-cel at the National Cancer Center Hospital (NCCH), Tokyo, Japan. We aimed to evaluate the long-term clinical efficacy and safety following tisa-cel infusion, with a focus on sustained cellular and humoral immune impairment in long-term survivors.

Materials and Methods

Patient selection

Patients were eligible for inclusion if they met all of the following criteria: (1) histologically confirmed LBCL treated at the NCCH; (2) underwent leukapheresis for tisa-cel between April 2020 and December 2024; and (3) received infusion of tisa-cel. Patients who received out-of-specification products were excluded. LBCL subtypes included diffuse large B cell lymphoma (DLBCL) not otherwise specified (NOS), DLBCL transformed from low-grade B cell lymphomas and high-grade B cell lymphoma (HGBCL), according to the 5th edition of WHO classification [11].

Data collection and definitions

Clinical data were collected retrospectively from electronic medical records. Disease status was assessed by contrast-enhanced computed tomography (CT) or positron emission tomography–computed tomography (PET-CT) scans performed at approximately 1, 3, 6, 12, 24, and 36 months post-infusion, or as clinically indicated. Responses to bridging therapy and tisa-cel were evaluated based on the Lugano classification [12]. Primary refractory LBCL was defined as the failure to achieve CR or partial response (PR) after front-line treatment or relapse within 12 months of achieving CR [13, 14]. Relapsed LBCL was defined as disease progression in patients who had previously responded (CR or PR) to treatment. Refractory LBCL was defined as failure to respond to the last line of treatment before CAR T-cell therapy [15, 16]. Toxicity assessment and management of cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS) were based on the American Society for Transplantation and Cellular Therapy (ASTCT) consensus criteria and the Expert Panel Opinion [17–20]. Immune parameters, including $CD4^+$ T-cell counts, $CD19^+$ B-cell counts, and serum IgG levels, were

measured at baseline and approximately 1, 3, 6, 12, 24, and 36 months after tisa-cel infusion, depending on clinical status and physician discretion. A “low $CD4^+$ T-cell count” was defined as an absolute $CD4^+$ T-cell count < 200 cells/μL, and a “low $CD19^+$ B-cell count” was defined as an absolute $CD19^+$ B-cell count < 50 cells/μL. Hypogammaglobulinemia was defined as a serum IgG concentration < 400 mg/dL.

Statistical Analysis

PFS was defined as the time from infusion to disease progression or death from any cause. OS was measured from infusion to death from any cause. Survival outcomes were estimated using the Kaplan–Meier method and compared using log-rank tests. Continuous variables were summarized as medians with ranges. Analyses were conducted using EZR (Jichi Medical University, Saitama, Japan) [21].

This study was approved by the Ethics Committe of the National Cancer Center. The requirement for written informed consent was waived owing to the retrospective nature of the study.

Results

Patient Characteristics

A total of 24 patients underwent leukapheresis for tisa-cel. Two patients did not receive infusion due to progressive disease (PD), and one patient experienced manufacturing failure and subsequently received another commercial CAR T-cell product (Fig. 1). Of the 21 patients who received tisa-cel infusion, the median age was 70 years (range, 36–79 years); 11 (52.4%) were male, and one patient (4.8%) presented with Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≥ 2. Three patients (14.3%) had a history of central nervous system (CNS) involvement, although none had active CNS disease at the time of leukapheresis (Table 1). The median number of prior treatment lines was three (range, 2–8), and six patients (28.6%) had previously undergone autologous stem cell transplantation (ASCT). Nine patients (42.9%) were primary refractory, and 16 (76.2%) were refractory before receiving tisa-cel. Elevated lactate dehydrogenase (LDH) levels were observed in 12 patients (57.1%). The median time from apheresis to tisa-cel infusion was 55 days (range, 44–85). Eighteen patients (85.7%) received bridging therapy prior to infusion, most commonly multi-agent salvage chemotherapy regimens with or without rituximab (n = 9, 50.0%), followed by polatuzumab vedotin plus bendamustine with or without rituximab (n = 3). Of the remaining six patients, two received rituximab monotherapy and four underwent radiotherapy.

Response and Survival

At one month post-infusion, the ORR was 61.9% (13 of 21 patients), with 12 patients (57.1%) achieving CR (Table 2). At 3 months after infusion, the ORR and CR rates were both 52.4% (11/21). At a median follow-up of 3.2 years, the 3-year PFS was 42.9% (median 18.3 months, 95% CI 1.4–NR) and the 3-year OS was 62.2% (median not reached, 95%CI 11.1-NR) (Fig. 2). Among 12 patients who relapsed, biopsy at

relapse was performed in 10 (83.3%). CD19 remained positive in 6 patients (60.0%), negative in 1 patient (10.0%), while it was not evaluated in 3 patients. At the data cut-off, seven patients had died, all due to disease progression. Patients who achieved a response at 6 months subsequently demonstrated durable responses (Fig. 3).

Safety

CRS occurred in 16 of 21 patients (76.2%). Most events were grade 1 (n = 8, 38.1%) or grade 2 (n = 7, 33.3%); only one patient (4.8%) experienced grade 3 CRS, and no grade ≥ 4 events were observed (Table S1). The median time to CRS onset was 2 days (range, 2–6 days), and the median duration was 4 days (range, 2–9 days). Tocilizumab was administered to 11 patients (52.4%), with a median initiation time of 2 days (range, 1–5 days) after onset. Corticosteroids were used in 5 patients (23.8%). ICANS was not observed in any patient.

Immune Reconstitution

Peripheral blood lymphocyte subsets were evaluated immediately before lymphodepleting (LD) chemotherapy and following tisa-cel infusion. $CD4^+$ T-cell counts were reduced prior to LD chemotherapy (median 229 cells/μL, range 22–512) (Table S2). Long-term monitoring revealed delayed immune recovery (Fig. 4A). $CD4^+$ T-cell counts gradually increased, and $CD4^+$ T-cell recovery was achieved in 70.0% of CR survivors at 1 year. However, recovery was not always sustained; although some patients transiently exceeded the 200-cells/μL threshold, their counts fluctuated and subsequently fell below this level (Table S2). For example, $CD4^+$ T-cell counts in patient_ID_2 fluctuated around the 200 cells/μL during the first year, stabilizing above the threshold only after the second year. In patient_ID_6, an initial $CD4^+$ T-cell recovery at 3 months was followed by a decline to < 200 cells/μL at 12 months; sustained recovery (≥ 200 cells/μL) was eventually maintained at 3 years. Ultimately, all 8 CR patients evaluable at 3 years achieved $CD4^+$ T-cell recovery (median 569 cells/μL, range 205–771). $CD19^+$ B-cell reconstitution was incomplete in most cases (Table S3). $CD19^+$ B-cell counts remained below 50 cells/μL in 7 of 10 evaluable CR patients (70.0%) at 1 year, 5 of 7 (71.4%), and 4 of 6 (66.7%) at 3 years (Fig. 4B). Hypogammaglobulinemia (IgG < 400 mg/dL) was observed in 4 of 21 patients (19.0%) prior to LD chemotherapy (Table S4). Serum IgG levels gradually decreased during follow-up period, with hypogammaglobulinemia persisting in 2 of 11 evaluable CR patients (18.2%) at 1 year (median, 571 mg/dL; range 310–960 mg/dL), 2 of 9 (22.2%) at 2 years (median, 383 mg/dL, range 272–1157 mg/dL), and 4 of 7 (57.1%) at 3 years (median, 383 mg/dL, range 247–704 mg/dL) (Fig. 4C).

Despite the high prevalence of prolonged immune impairment, serious infections were infrequent in this cohort. Three patients (14.3%) developed COVID-19, of whom two had mild and one had moderate disease; no severe cases were observed. Other infectious complications occurred in three patients (14.3%) (Table S5). No opportunistic infections such as *Pneumocystis jirovecii* pneumonia (PJP) were documented.

Discussion

In this single-center retrospective analysis, we report, to our knowledge, the longest follow-up of commercial tisa-cel use in Japanese patients with r/r LBCL. With a median follow-up of 3.2 years, tisa-cel demonstrated a durable benefit, with 3-year OS and PFS rates of 62.3% and 42.9%, respectively. These outcomes are broadly comparable to, and in some respects favorable relative to, those reported in other real-world registries and clinical cohorts, despite the relatively older age and high proportion of refractory disease in our cohort (Table S6) [2–10]. Our findings thus support the long-term effectiveness of second-generation CAR-T therapy in routine clinical practice in Japan.

In the present study, we comprehensively evaluated long-term immune reconstitution following tisa-cel therapy and compared our findings with previously published real-world CD19-targeted CAR-T studies (Table 3). Notably, our cohort represents one of the longest follow-up durations reported to date, enabling a detailed assessment of late immune recovery.

We observed that 30% of CR survivors had not yet achieved $CD4^+$ T-cell recovery at 1 year after infusion, a proportion broadly consistent with previous CD19-targeted CAR-T reports [22–24]. However, $CD4^+$ T-cell recovery was ultimately achieved in all evaluable CR patients by three years. In contrast, B-cell reconstitution was markedly impaired and often prolonged. In published cohorts, only about 10% of patients have detectable peripheral B cells at one month, rising to roughly 20% by three months and about half by 6 to 12 months [22, 25]. B-cell reconstitution in our cohort appeared more delayed than previously reported, with only 30.0% of evaluable CR patients achieved B-cell reconstitution at 1 year. Notably, recovery remained limited even with longer follow-up, with B-cell reconstitution observed in only 28.6% at 2 years and 33.3% at 3 years.

Consistent with impaired B-cell recovery, hypogammaglobulinemia was also prolonged. Hypogammaglobulinemia is frequently observed even before CAR-T infusion, reflecting cumulative immunosuppression from prior therapies, and IgG levels typically decline further after infusion, with 48–61% of patients exhibiting IgG levels < 400 mg/dL at 1 year [25, 26]. Extending these observations, we found that hypogammaglobulinemia persisted in a substantial proportion of long-term survivors, with 57.1% of evaluable patients still demonstrating IgG levels < 400 mg/dL at 3 years.

Taken together, our results indicate that immune reconstitution is a slow, long-term process, characterized by progressive $CD4^+$ T-cell recovery over several years juxtaposed with sustained B-cell aplasia with long-lasting hypogammaglobulinemia. These findings have important implications for infection risk, vaccination strategies, and the need for individualized long-term supportive care in CAR-T survivors.

Differences in immune reconstitution according to the CAR costimulatory domain have been increasingly recognized. Tisa-cel is a 4-1BB–based CAR-T product, and prior studies have suggested delayed B-cell recovery compared with CD28-based products, such as axicabtagene-ciloleucel (axi-cel) (Table 3). Specifically, $CD19^+$ B-cell detectable at 1 year after infusion were observed in 32.2% of patients treated

with CD28-based CAR-T products, whereas this was seen in only 5.9% of patients receiving 4-1BB–based products [24]. In addition, the duration of B-cell aplasia has been reported to be significantly longer with 4-1BB–based product (median, 278 days) than with CD28-based therapy (median, 165 days) [26]. Our findings are consistent with these observations, demonstrating durable B-cell aplasia and prolonged hypogammaglobulinemia in patients treated with tisa-cel. Notably, 4-1BB–based CAR-T cells have been shown to persist beyond one year after infusion, which may mechanistically explain the sustained suppression of B-cell reconstitution observed in tisa-cel–treated patients [27].

In this study, prophylaxis against PJP was generally continued for at least 12 months or until $CD4^+$ T-cell counts exceed 200 cells/μL, while antiviral prophylaxis against herpes simplex virus and varicella-zoster virus reactivation is maintained for approximately 12 months. In addition, intravenous immunoglobulin replacement was administered to patients with IgG levels below 400 mg/dL. By adhering to these prophylactic strategies and carefully monitoring immune recovery, no severe infectious events were observed in our cohort. These findings are consistent with current guideline recommendations and emphasize the importance of confirming sustained immune recovery before discontinuing prophylactic regimens [23, 28].

Our study is limited by its retrospective, single-center design and small sample size, which precluded multivariable analyses. Nevertheless, the consistency of institutional practice and the availability of longitudinal follow-up provide valuable real-world insights.

In conclusion, tisa-cel provided durable long-term disease control with an acceptable safety profile in Japanese patients with r/r LBCL treated in routine clinical practice. Importantly, extended follow-up revealed sustained immune impairment, particularly prolonged B-cell aplasia and hypogammaglobulinemia, even among long-term responders. These findings emphasize the necessity of standardized long-term immune monitoring and individualized supportive care strategies to optimize survivorship care following CAR T-cell therapy.

Declarations

Acknowledgments

We thank the clinical staff of the Department of Hematology, National Cancer Center Hospital, for their support in patient care and data collection.

Author contributions

F. Yoshino and S. Makita designed the research; are the principal investigators; treated patients; and wrote the manuscript, reviewed its final version, and take primary responsibility for it.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest

Conflict Of Interest Disclosure:

SM received honoria for lectures from Chugai Pharmaceutical Co., Bristol Myers Squibb, Gilead Sciences and Genmab.

SF received research funding from LOXO Oncology, AbbVie, Chugai Pharmaceutical Co. and Mitsubishi Tanabe Pharma Co.

WM received research finding from Genmab, Nippon Shinyaku Co. and Ono Pharmaceutical Co.

KI (Izutsu) has received research funding from AstraZeneca, AbbVie, Incyte, SymBio, Bristol Myers Squibb, Bayer, Pfizer, Janssen, Yakult, Kyowa Kirin, Ono Pharmaceutical, Daiichi Sankyo, Chugai Pharmaceutical Co., BeOne Medicines, Genmab, LOXO Oncology, Otsuka, Regeneron, Gilead Sciences, and MSD. KI has received honoraria from Chugai Pharmaceutical Co., AbbVie, BeOne Medicines, Gilead Sciences, Bristol Myers Squibb, AstraZeneca, Nippon Shinyaku, Ono Pharmaceutical, Johnson & Johnson, Kyowa Kirin, Genmab, Otsuka, Eisai, SymBio, MSD, Eli Lilly, and Recordati. KI has also received consultancy fees from Chugai Pharmaceutical Co., AbbVie, BeOne Medicines, Bristol Myers Squibb, AstraZeneca, Nihon Shinyaku, Genmab, Ono Pharmaceutical, Mitsubishi Tanabe Pharma, Kyowa Kirin, Otsuka, Zenyaku, Daiichi Sankyo, Eisai, and Takeda.

No other authors declare conflicts of interest associated with this manuscript.

References

1. Schuster SJ, Tam CS, Borchmann P, Worel N, McGuirk JP, Holte H, et al. Long-term clinical outcomes of tisagenlecleucel in patients with relapsed or refractory aggressive B-cell lymphomas (JULIET): a multicentre, open-label, single-arm, phase 2 study. Lancet Oncol. 2021;22: 1403–1415.
2. Landsburg DJ, Frigault MJ, Heim M, Foley SR, Hill B, Schofield G, et al. Real-world outcomes with tisagenlecleucel in aggressive B-cell lymphoma: subgroup analyses from the CIBMTR registry. J Immunother Cancer. 2025;13: e009890.
3. Trando A, Ter-Zakarian A, Yeung P, Goodman AM, Hamdan A, Hurley M, et al. Outcomes of chimeric antigen receptor (CAR) T-cell therapy in patients with large B-cell lymphoma (LBCL): A single-institution experience. Cancers (Basel). 2023;15: 4671.
4. Goto H, Kitawaki T, Fujii N, Kato K, Onishi Y, Fukuhara N, et al. Safety and efficacy of tisagenlecleucel in patients with relapsed or refractory B-cell lymphoma: the first real-world evidence in Japan. Int J Clin Oncol. 2023;28: 816–826.

5. Chihara D, Liao L, Tkacz J, Franco A, Lewing B, Kilgore KM, et al. Real-world experience of CAR T-cell therapy in older patients with relapsed/refractory diffuse large B-cell lymphoma. Blood. 2023;142: 1047–1055.
6. Jacobson CA, Munoz J, Sun F, Kanters S, Limbrick-Oldfield EH, Spooner C, et al. Real-world outcomes with chimeric antigen receptor T cell therapies in large B cell lymphoma: A systematic review and meta-analysis. Transplant Cell Ther. 2024;30: 77.e1–77.e15.
7. Yoon SE, Cho J, Cho D, Kang E-S, Kim SJ, Kim WS. Clinical outcomes of tisagenlecleucel in relapsed/refractory diffuse large B-cell lymphoma: insights from a single-center study. Int J Hematol. 2025;122: 533–545.
8. Ho PJ, Vanguru V, Burge CS, Wayte R, Brown C, Bryant CE, et al. Real-world Australian experience with tisagenlecleucel for relapsed/refractory diffuse large B-cell lymphoma-importance of pre-CAR-T optimization. Front Oncol. 2025;15: 1633644.
9. Liao L, Nastoupil L, Wilson L, Flores Avile C, Kilavuz T, Chen L. P1182: Real-world characteristics and clinical outcomes in relapse/refractory diffuse large b-cell lymphoma patients who received car-t therapy. HemaSphere. 2022;6: 1068–1069.
10. Iacoboni G, Villacampa G, Martinez-Cibrian N, Bailén R, Lopez Corral L, Sanchez JM, et al. Real-world evidence of tisagenlecleucel for the treatment of relapsed or refractory large B-cell lymphoma. Cancer Med. 2021;10: 3214–3223.
11. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, de Oliveira Araujo IB, Berti E, et al. Correction: “the 5th edition of the world health organization classification of haematolymphoid tumours: Lymphoid neoplasms” leukemia. 2022 Jul;36(7):1720-1748. Leukemia. 2023;37: 1944–1951.
12. Cheson BD, Fisher RI, Barrington SF. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32: 3059–3068.
13. Bock AM, Mwangi R, Wang Y, Khurana A, Maurer MJ, Ayers A. Defining primary refractory diffuse large B-cell lym- phoma (DLBCL) based on survival outcomes. Hematol Oncol. 2023;41: 430–432.
14. Bock AM, Mwangi R, Wang Y, Khurana A, Maurer MJ, Ayers A, et al. Defining primary refractory large B-cell lymphoma. Blood Adv. 2024;8: 3402–3415.
15. Vpennings E, Durmaz M, Visser O, Posthuma E, Issa DE, Chamuleau M. Treatment and outcomes for patients with relapsed or refractory diffuse large B-cell lymphoma: a contemporary, nationwide, population-based study in the Netherlands. Blood Cancer J. 2024;14.
16. Raut LS, Chakrabarti PP. Management of relapsed-refractory dif- fuse large B cell lymphoma. South Asian J Cancer. 2014;3.
17. Kanate AS, Majhail NS, Savani BN, Bredeson C, Champlin RE, Crawford S. Indications for hematopoietic cell transplantation and immune effector cell therapy: guidelines from the ameri- can society for transplantation and cellular therapy. Biol Blood Marrow Transplant. 2020;26: 1247–1256.
18. Lee DW, Santomasso BD, Locke FL. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019;25:

625–638.

19. Jain T, Bar M, Kansagra AJ. Use of chimeric antigen receptor T cell therapy in clinical practice for relapsed/refractory aggressive B cell non-Hodgkin lymphoma: an expert panel opin- ion from the American Society for Transplantation and Cellular Therapy. Biol Blood Marrow Transplant. 2019;25: 2305–2321.
20. Bachanova V, Bishop MR, Dahi P, Dholaria B, Grupp SA, Hayes-Lattin B, et al. Chimeric antigen receptor T cell therapy during the COVID-19 pandemic. Biol Blood Marrow Transplant. 2020;26: 1239–1246.
21. Kanda Y. Investigation of the freely available easy-to-use software “EZR” for medical statistics. Bone Marrow Transplant. 2013;48: 452–458.
22. Baird JH, Epstein DJ, Tamaresis JS, Ehlinger Z, Spiegel JY, Craig J, et al. Immune reconstitution and infectious complications following axicabtagene ciloleucel therapy for large B-cell lymphoma. Blood Adv. 2021;5: 143–155.
23. Wudhikarn K, Palomba ML, Pennisi M, Garcia-Recio M, Flynn JR, Devlin SM, et al. Infection during the first year in patients treated with CD19 CAR T cells for diffuse large B cell lymphoma. Blood Cancer J. 2020;10: 79.
24. Stock S, Bücklein VL, Blumenberg V, Magno G, Emhardt A-J, Holzem AME, et al. Prognostic significance of immune reconstitution following CD19 CAR T-cell therapy for relapsed/refractory B-cell lymphoma. HemaSphere. 2025;9. doi:10.1002/hem3.70062
25. Logue JM, Zucchetti E, Bachmeier CA, Krivenko GS, Larson V, Ninh D, et al. Immune reconstitution and associated infections following axicabtagene ciloleucel in relapsed or refractory large B-cell lymphoma. Haematologica. 2021;106: 978–986.
26. Sutherland NM, Zhou B, Zhang L, Ong M-S, Hong JS, Pak A, et al. Association of CD19+-targeted chimeric antigen receptor (CAR) T-cell therapy with hypogammaglobulinemia, infection, and mortality. J Allergy Clin Immunol. 2025;155: 605–615.
27. Schuster SJ, Svoboda J, Chong EA, Nasta SD, Mato AR, Anak Ö, et al. Chimeric antigen receptor T cells in refractory B-cell lymphomas. N Engl J Med. 2017;377: 2545–2554.
28. Baden LR, Swaminathan S, Almyroudis NG, Angarone M, Baluch A, Barros N, et al. Prevention and treatment of cancer-Related Infections, version 3.2024, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2024;22: 617–644.

Tables

Tables 1 to 3 are available in the Supplementary Files section.

Figures

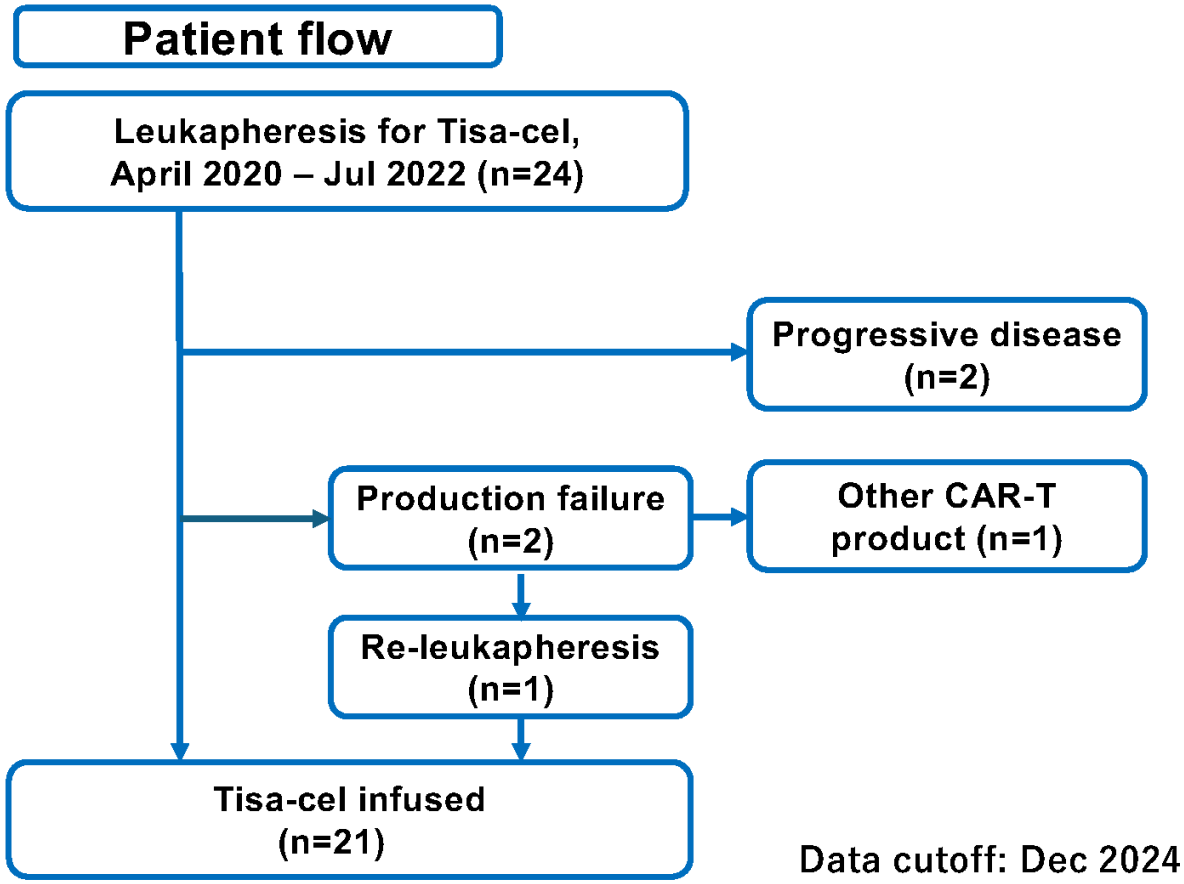


Figure 1

Cohort description

Patient flow diagram of the study. Between April 2020 and July 2022, 24 patients underwent leukapheresis for tisa-cel manufacturing. Among them, 21 patients received tisa-cel infusion. Reasons for non-infusions included progressive disease (PD, n=2) and manufacturing failure (n=2). Of the patients with manufacturing failure, one underwent re-leukapheresis and the other received an alternative CAR-T product. The data cutoff was December, 2024.

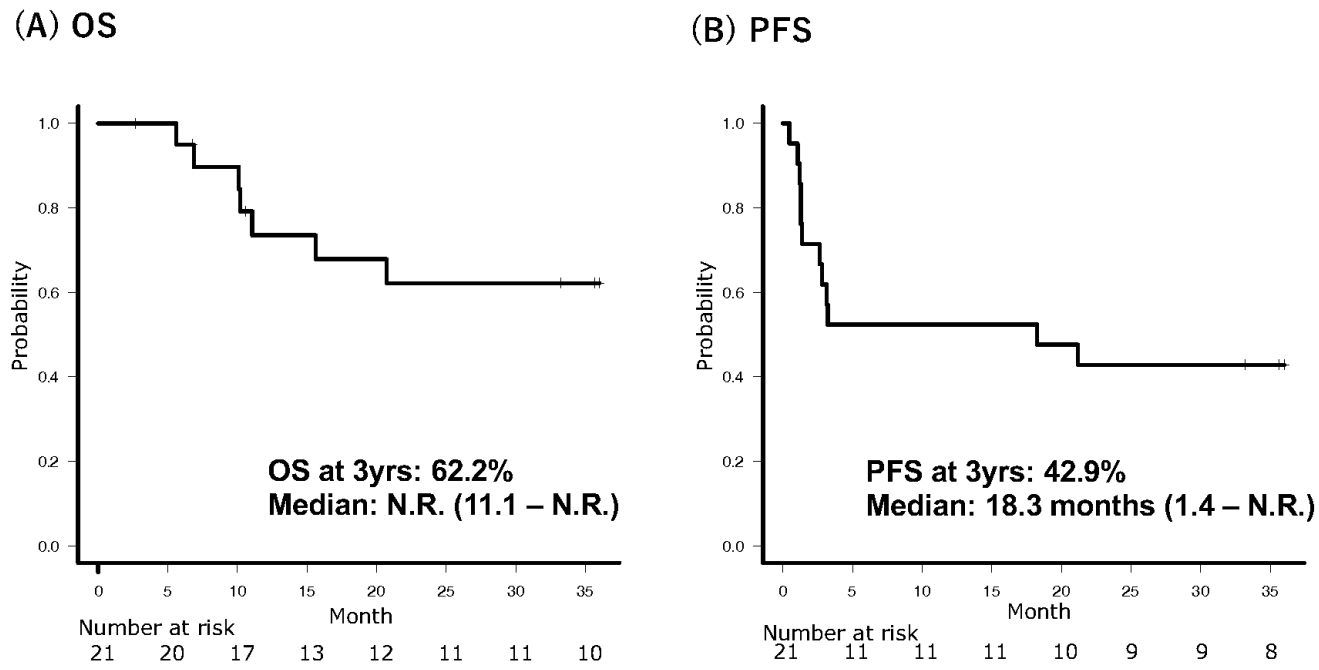


Figure 2

Clinical outcomes after tisa-cel infusion

Kaplan–Meier curves showing (A) progression-free survival (PFS) and (B) overall survival (OS) in patients with r/r LBCL. PFS was defined as the time from infusion to disease progression or death from any cause; and OS was defined as the time from infusion to death from any cause. Tick marks indicate censored observations. The median follow-up among survivors was 3.2 years.

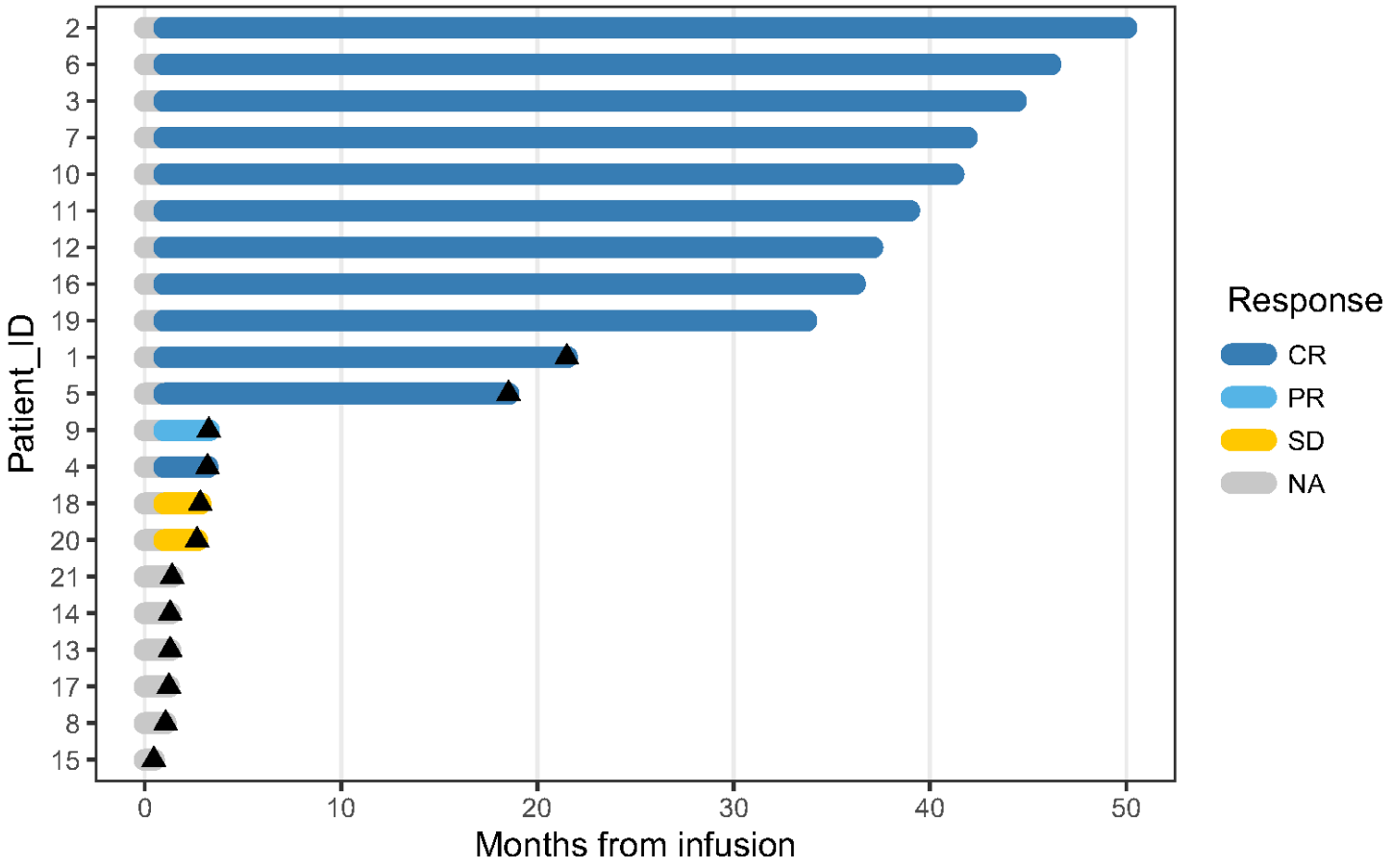


Figure 3

Swimmer plot of clinical course after tisa-cel

Swimmer plot illustrating individual patient clinical courses following tisa-cel infusion. Each horizontal bar represents one patient, with time measured from infusion to last follow-up or PD. Symbols and color coding indicate clinical responses: CR, complete response; PR, partial response; SD, stable disease; and NA, not assessable. Triangles indicate PD.

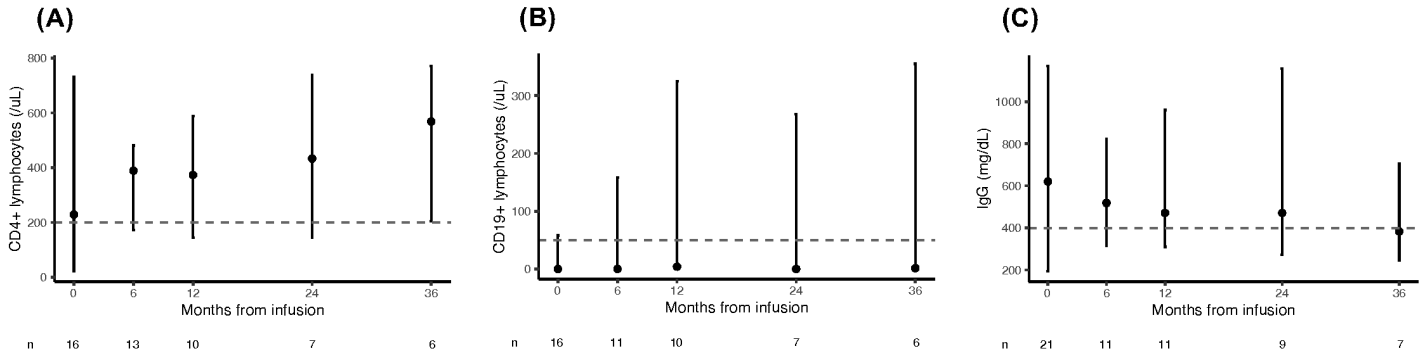


Figure 4

Longitudinal immune reconstitution following tisa-cel infusion. Median values with ranges (minimum–maximum) are shown for (A) $CD4^+$ T-cell counts, (B) $CD19^+$ B-cell counts, and (C) serum IgG levels at baseline (pre-LD) and6, 12, 24, and 36 months after infusion. The number of evaluable CR patients at each time point is shown below the x-axis. The numbers of patients with $CD4^+$ T-cell counts <200 cells/μL, $CD19^+$ B-cell counts <50 cells/μL, and IgG levels <400 mg/dL are indicated beneath each panel.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.pdf
- Table2.pdf
- Table3.pdf
- TableS1.pdf
- TableS2.pdf
- TableS3.pdf
- TableS4.pdf
- TableS5.pdf
- TableS6.pdf
- supptablelegends.docx