Anti-CD19 CAR T-cell therapy in relapsed/refractory T-cell/histiocyte-rich large B-cell lymphoma: insights from the French DESCAR-T registry, a LYSA study

T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL) is an uncommon variant of diffuse large B-cell lymphoma (DLBCL) that typically affects younger male patients and is characterized by widespread disease at diagnosis and an immunologically tolerogenic tumor microenvironment. While introduction of rituximab has improved outcomes to levels approaching those of DLBCL overall, prognosis of relapsed or refractory (R/R) THRLBCL remains poor.[1-3] Chimeric antigen receptor (CAR) T-cell therapy has transformed the management of R/R DLBCL, becoming a standard second- and third-line option; however, its efficacy in THRLBCL has not been clearly defined, as this subgroup was underrepresented in pivotal trials.[4-6] Leveraging data from the French DESCAR-T registry, we evaluated efficacy and safety of anti-CD19 CAR T-cell therapy in 23 patients with R/R THRLBCL, all of whom underwent centralized pathology review. Although overall efficacy was modest, with a 3-month complete remission (CR) rate of 32% and a median progression-free survival (PFS) of 3.1 months, patients achieving CR experienced durable responses, some of which exceeded 3 years. These results suggest that, despite limited overall efficacy, a subset of THRLBCL patients may derive long-term benefit from CAR T-cell therapy, underscoring the need to refine therapeutic strategies and explore rational combinations.

Patients with R/R THRLBCL treated with CAR T-cell therapy were identified from the French national DESCAR-T registry (NCT04328298), which prospectively includes all CAR T-cell–treated patients in France. Data were collected from patients treated from July 2018 to March 2024. All diagnoses were established within the Lymphopath network and pathological reports underwent centralized independent review by expert hematopathologists to confirm THRLBCL.[7] Baseline clinical and biological characteristics were collected at infusion. Efficacy outcomes included overall and CR rates, PFS, overall survival (OS), and duration of response. Response was assessed according to international criteria. Survival estimates were calculated using the Kaplan–Meier method, and proportions were reported with 95% confidence intervals. The DESCAR-T registry complies with the French legal requirements of Research Not Involving the Human Person and data reuse (RNIPH-MR004). As such, before their enrollment in the DESCAR-T registry, all patients or their legal representatives were individually informed about the non-interventional use of personal data.

Among 3,080 patients in DESCAR-T at the time of data export, 23 had received CAR T-cell therapy for R/R THRLBCL and were included in the analysis. Most were male (N=20), with a median age at time of CAR T-cell infusion of 49 years (range, 25-76). A history of low-grade lymphoma was noted in seven patients (6 nodular lymphocyte-predominant Hodgkin lymphomas, and 1 marginal zone lymphoma) with THRLBCL. Most patients had Ann-Arbor stage III-IV disease (N=21), three had bulky disease (defined as largest lesion >5 cm) and 17 presented with refractory disease at the time of CAR T-cell therapy. Central nervous system involvement was ruled out in two patients and was not investigated in the other 21. All had received prior anti-CD20 monoclonal antibody treatment plus chemotherapy; additional treatments included radiotherapy (N=2), immunomodulatory drugs (N=2), epigenetic modifiers (N=1), and other anti-lymphoma agents (N=2). Five had undergone autologous stem cell transplantation (ASCT). CAR T cells were administered as second- or third-line therapy in 15 patients, and as fourth-line or later in eight patients. Seventeen patients received bridging therapy, primarily anti-CD20 monoclonal antibody plus chemotherapy (N=12), lenalidomide-based therapy (N=2), immune checkpoint inhibitor (pembrolizumab) (N=2), or radiotherapy plus chemotherapy (N=1). At the time of CAR T-cell infusion, 12 patients had progressive disease, six had stable disease or partial response, and three had achieved CR. Eastern Cooperative Oncology Group performance status at CAR T-cell infusion was preserved (0-1) in 19 patients, lactate dehydrogenase level was increased in 12 patients and ferritin level was high in 15. All patients received lymphodepletion with fludarabine and cyclophosphamide, followed by axicabtagene ciloleucel (N=14), tisagenlecleucel (N=8), or lisocabtagene maraleucel (N=1). The patients' characteristics are summarized in Table 1.

At 3 months after CAR T-cell therapy, among 22 evaluable patients, 14 had progressive disease, one had achieved a partial response and seven had achieved a CR, representing an overall response rate of 36% (95% confidence interval [95% CI]: 17–59) and a CR rate of 32% (95% CI: 14–55). At 12 months, among 21 evaluable patients, the CR rate was 19% (95% CI: 5-42). Overall, relapse occurred in 16 patients (assessed by positron emission tomography in 8 patients and by an unknown method in the other 8 patients), with a median time to relapse of 2.4 months (interquartile range, 1.0-3.1). Among 16 patients who relapsed after CAR T-cell therapy, 15 received subsequent therapies and three achieved a partial or complete response. Among R/R patients after CAR T-cell therapy, seven remained alive after 1 year, having received lenalidomide

and anti-CD20 monoclonal antibody (N=3), lenalidomide, ibrutinib and anti-CD20 monoclonal antibody (N=1), an immune checkpoint inhibitor and ASCT (N=1), an immune checkpoint inhibitor alone (N=1) or a bispecific anti-CD20/CD3 monoclonal antibody (N=1). Outcome and treatments received for all patients are summarized in Figure 1.

The median follow-up was 22.8 months (95% CI: 11.6-37.7), the median PFS was 3.1 months (95% CI: 2.0-12.0) and the median OS was 22.4 months (95% CI: 5.0-not reached). At 1-year, the estimated PFS was 32% (95% CI: 14-51) and estimated OS was 63% (95% CI: 40-80). Among responders, the median duration of response was 10.5 months (95% CI: 1.4-NA). In patients achieving a CR, the median duration of CR was 36.2 months (95% CI: 1.0-NA). In relapsed patients, no clear benefit was observed with immune checkpoint inhibition after CAR T-cell therapy. These data and associated survival curves are shown in Figure 2. Association of low-grade lymphoma with THRLBCL had no impact on PFS after CAR T-cell therapy (log-rank *P*=0.11) (*Online Supplementary Figure S1*).

During follow-up, ten patients died: nine due to disease progression and one from an unknown cause.

Toxicity was consistent with expectations: 19 patients experienced CAR T-cell-specific toxicities, with cytokine release syndrome in 18 patients, including one case of grade 3-4 cytokine release syndrome, with a median onset of 2.5 days (range, 0-8.0) after the infusion. Immune effector cell-associated syndrome (ICANS) occurred in 8 patients, including two cases of grade 3-4 syndrome, with a median onset of 6.0 days (range, 1.0-9.0) after the infusion. Grade 3 infections were reported in 12 patients. No unexpected toxicities or treatment-related deaths occurred.

With a 3-month CR rate of 32% and median PFS of 3.1 months, our findings reaffirm the limited efficacy of CAR T-cell therapy in R/R THRLBCL, consistent with prior reports. Early analyses by Nair *et al*. and Trujillo *et al*. similarly demonstrated modest therapeutic activity, with low response rates and short PFS.[8,9] In the largest cohort to date, the Center for International Blood and Marrow Transplant Research (CIBMTR) reported a 2-year PFS of 29% and a 2-year OS of 42%.[10] More recently, the Spanish cooperative group, using the GELTAMO/GETH-TC registry, described comparable outcomes.[11] Despite overall modest results, our data showed that CAR T-cell therapy may offer substantial benefit to selected patients. Thus, those who achieved CR demonstrated prolonged response, with a median duration of CR of 36.2 months. Nevertheless, the limited sample size precluded identification of factors predictive of durable benefit. Similarly, no clinical variables associated with improved survival were identified in the CIBMTR cohort. These findings emphasize prudent patient selection in THRLBCL based on known risk factors such as high tumor burden and inflammation, yet do not support withholding CAR T-cell therapy, as many patients may still achieve durable benefit.

Notably, we observed a discrepancy between sustained OS (1-year OS of 63%) and relatively short PFS (1-year PFS of 32%), suggesting that effective subsequent therapies may

Table 1. Characteristics of the patients at baseline and at the time of chimeric antigen receptor T-cell infusion.

Characteristics	N (%)
Males	20 (87)
Age at 1st CAR T-cell infusion, years, median (min-max)	49 (25-76)
18-64	18 (78)
65-75	4 (17)
> 75	1 (4)
Age-adjusted IPI at diagnosis of THRLBCL	
0	1 (4)
1	3 (13)
2	15 (65)
3	0 (0)
Missing	4 (17)
Ann-Arbor Stage at diagnosis of THRLBCL	
I-II	1 (4)
III-IV	21 (19)
Missing	1 (4)
Diagnosis of low-grade lymphoma during history of THRLBCL	
No	16 (70)
Yes	7 (30)
At least one comorbidity according to HCT-CI	
No	19 (83)
Yes	4 (17)
N of prior lines of therapy before 1st CAR T-cell infusion median (min-max)	2 (1-10)
1	3 (13)
2	12 (52)
≥ 3	8 (35)
Prior autologous transplant before 1st CAR T-cell infusion	
No	18 (78)
Yes	5 (22)
Disease status at time of CAR T-cell decision	
Refractory	17 (74)
Relapse	5 (22)
Missing	1 (4)
Bridging therapy before CAR T-cell infusion	
No	6 (26)
Yes†	17 (74)
Disease status after bridging therapy before 1st CAR T-cell infusion	
Complete response	3 (18)
Partial response	5 (29)
Stable disease	1 (6)
Progressive disease	6 (35)
Not evaluated	2 (12)

†Bridging therapy used was anti-CD20 monoclonal antibody plus chemotherapy (N=12), lenalidomide-based therapy (N=2), immune checkpoint inhibitors (N=2), or radiotherapy plus chemotherapy (N=1). Percentages may not total 100% due to rounding. CAR: chimeric antigen receptor; IPI: International Prognostic Index; HCT-CI: Hematopoietic Cell Transplantation-specific Comorbidity Index; THRLBCL: T-cell/histiocyte-rich large B-cell lymphoma.

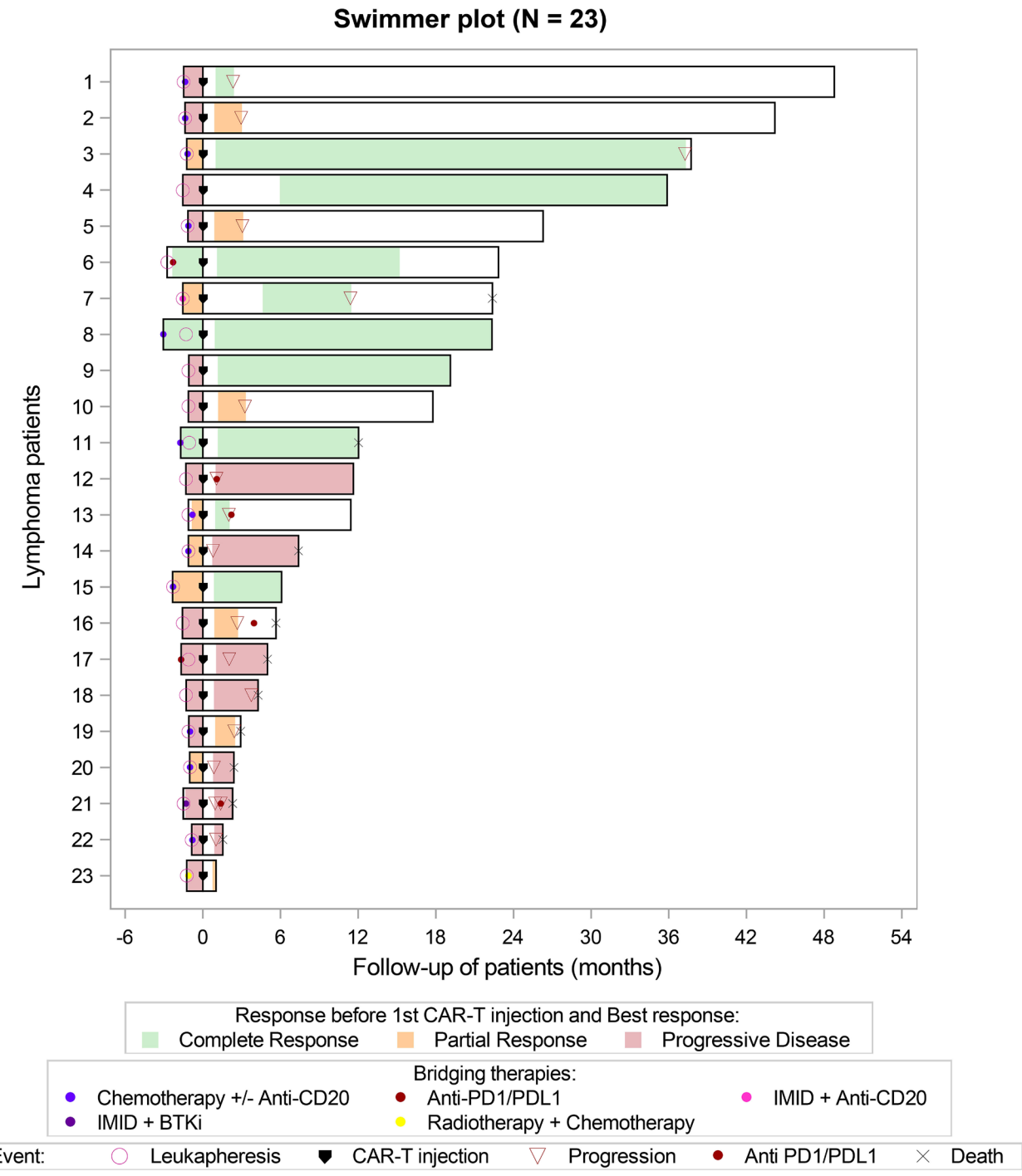


Figure 1. Swimmer-plot depiction of treatment sequence, disease course, and survival in all 23 patients. BTKi: Bruton tyrosine kinase inhibitor (here the only BTKi used was ibrutinib); CAR: chimeric antigen receptor; IMID: immunomodulatory drug (here the only IMID used was lenalidomide); PD1: programmed death protein 1; PDL1: programmed death ligand 1.

be contributing to prolonged survival following CAR T-cell therapy in THRLBCL. Trujillo *et al*. reported high expression of PD-1 and objective responses in two of five patients treated with anti–PD-1 therapy at progression after CAR T-cell therapy, hypothesizing that THRLBCL may possess an inherently CAR T-cell–resistant tumor microenvironment.[8] Similarly, among the 20 patients included in the national GELTAMO/GETH-TC registry, those who subsequently received immune checkpoint inhibitors or anti-CD20/anti-CD3 bispecific antibodies appeared to maintain better OS despite post-CAR T-cell relapse.[11] However, in our cohort, we did not observe an evident benefit of immune checkpoint inhibition despite PD-1 expression by T cells of the tumor microenvironment in five of six patients receiving immune checkpoint inhibitors. Interestingly, among the seven patients surviving at 1 year after CAR T-cell relapse, four had received lenalidomide-based treatments. Nevertheless, these retrospective and non-comparative data should be interpreted with caution and warrant validation in larger THRLBCL-specific cohorts.

The search for effective alternative therapies is equally pressing, particularly for patients ineligible for CAR-T-cell therapy. Data from the CIBMTR suggest that intensive chemotherapy followed by ASCT remains effective for chemosensitive patients, even in the CAR T-cell era.[12] The European Society for Blood and Marrow Transplantation (EBMT) has similarly reported that patients undergoing ASCT for R/R THRLBCL achieve particularly favorable outcomes compared with those of patients with other DLBCL subtypes, with a 2-year PFS rate of 78%.[13] Bispecific antibodies, alone or in combination with lenalidomide, represent promising options and are under active inves-

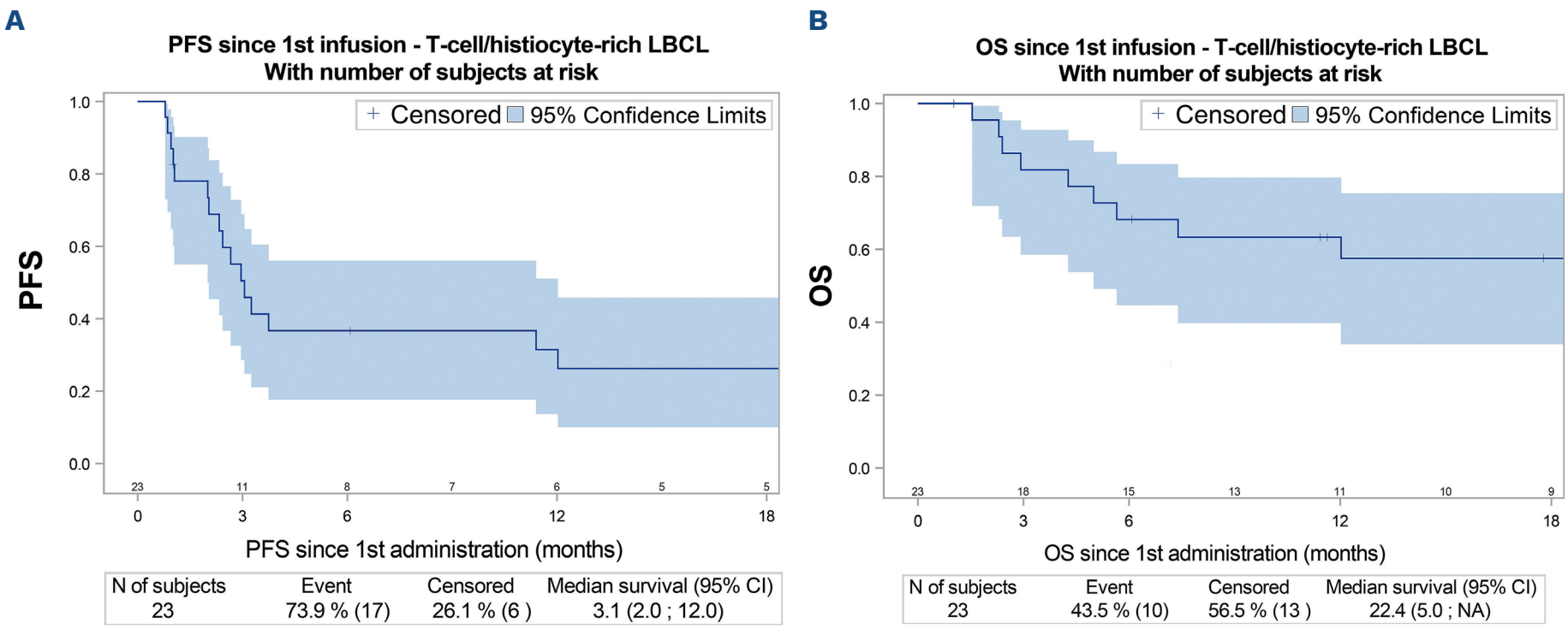


Figure 2. Survival outcomes and impact of anti-PD1/PDL1 treatment at relapse after chimeric antigen receptor T-cell therapy in T-cell/histiocyte-rich large B-cell lymphoma. Kaplan–Meier estimates of progression-free survival (PFS) and overall survival (OS) after chimeric antigen receptor (CAR) T-cell therapy, and PFS from relapse after CAR T-cell therapy (PFS2) according to receipt of anti-PD1/PDL1. (A) PFS for all 23 patients after CAR T-cell infusion. (B) OS for all 23 patients after CAR T-cell infusion. (C) PFS2 for patients who relapsed after CAR T-cell therapy and were treated (N=15), stratified by anti-PD1/PDL1 treatment *versus* other therapies. CI: confidence interval; LBCL: large B-cell lymphoma; NA: not reached; PD1: programmed death protein 1; PDL1: programmed death ligand 1.

tigation in R/R DLBCL settings.[14,15] Such regimens could represent an attractive alternative for patients with R/R THRLBCL.

Overall, although CAR T-cell therapy yields modest overall response rates in R/R THRLBCL, durable remissions are achievable in a subset of patients. Prioritizing the identification of likely responders and expanding therapeutic alternatives - including ASCT, bispecific antibodies, lenalidomide-based regimens, and immune checkpoint inhibitors, alone or in combination - will be essential to improve outcomes in this rare, challenging disease.

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https://doi.org/10.3324/haematol.2025.289196

Received: September 25, 2025.
Accepted: March 30, 2026.
Early view: April 9, 2026.

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Disclosures

AA has received travel support from Novartis. GC has received consulting fees from BMS/Celgene, Roche, Onwards Therapeutics, and MabQi; honoraria from Janssen, Takeda, AbbVie, Jansen, and Novartis; and meeting support from Roche and Janssen. RDB has received honoraria from and/or held advisory roles with Novartis, Kite/Gilead, Janssen, BMS-Celgene, and AbbVie. CC-L has received honoraria/travel and advisory fees from Gilead/Kite and Nektar Therapeutics. PB has received honoraria/travel support from AbbVie, Astellas, BMS/Celgene, Kite-Gilead, Novartis, and Servier. RH has received honoraria from Kite/Gilead, Novartis, BMS/Celgene, Incyte, Janssen, MSD, Takeda, Amgen, AbbVie, and Roche and has been a member of a Board of Directors or advisory committees for Kite/Gilead, Novartis, BMS/Celgene, Tessa Therapeutics, AbbVie, and Roche. FL has received honoraria from Takeda and AstraZeneca; has held advisory roles with Miltenyi, Kyowa Kirin, and BMS; has received travel support from Roche, Gilead, AbbVie, and Beigene; and has received research funding from BMS and Roche. EB, FM, AF, LR, AC, SG, GB, AC-M, EG, and CL have no conflicts of interest to disclose.

Contributions

AA, FL, and CL conceived and designed the study. AA wrote the article; AC-M performed the statistical analysis. CL supervised the pathology review of all cases. FL and CL supervised the study. All authors provided study material and patients, collected and assembled data, provided final approval for the article, and are accountable for all aspects of the work.

Acknowledgments

The authors thank the patients who accepted to be included in the DESCAR-T study, and all the investigators and their staff involved in the data collection and analyses. The authors thank everyone from the Lymphoma Academic Research Organization (LYSARC) DESCAR-T study group who actively participated in the study.

Funding

The DESCAR-T registry was partly funded by Gilead, Bristol Myers Squibb, and Novartis; however, they did not participate in the study design, data collection, statistical analysis, or interpretation, and did not provide assistance for manuscript writing or editorial support.

Data-sharing statement

All data generated or analyzed during this study are subject to controlled access by the Lymphoma Academic Research Organization (LYSARC) owing to privacy and legal requirements and proprietary reasons. LYSARC data can be re-used for the purposes of conducting research in the field of lymphoma after validation by the appropriate governing and scientific committees of The Lymphoma Study Association (LYSA). The author for correspondence can be contacted for data requests.

References

1. Delabie J, Vandenberghe E, Kennes C, et al. Histiocyte-rich B-cell lymphoma. A distinct clinicopathologic entity possibly related to lymphocyte predominant Hodgkin's disease, paragranuloma subtype. Am J Surg Pathol. 1992;16(1):37-48.
2. Bouabdallah R, Mounier N, Guettier C, et al. T-cell/histiocyte-rich large B-cell llymphomas and classical diffuse large B-cell lymphomas have similar outcome after chemotherapy: a matched-control analysis. J Clin Oncol. 2003;21(7):1271-1277.
3. Ollila TA, Reagan JL, Olszewski AJ, et al. Clinical features and survival of patients with T-cell/histiocyte-rich large B-cell lymphoma: analysis of the National Cancer Data Base. Leuk Lymphoma. 2019;60(14):3426-3433.
4. Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel as second-line therapy for Large B-cell lymphoma. N Engl J Med. 2022;386(7):640-654.
5. Abramson JS, Solomon SR, Arnason J, et al. Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study. Blood. 2023;141(14):1675-1684.
6. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017;377(26):2531-2544.
7. Laurent C, Baron M, Amara N, et al. Impact of expert pathologic review of lymphoma diagnosis: study of patients from the French Lymphopath network. J Clin Oncol. 2017;35(18):2008-2017.
8. Trujillo JA, Godfrey J, Hu Y, et al. Primary resistance to CD19-directed chimeric antigen receptor T-cell therapy in T-cell/histiocyte-rich large B-cell lymphoma. Blood. 2021;137(24):3454-3459.
9. Nair R, Ogundipe I, Gunther J, et al. Outcomes in patients with relapsed refractory T-cell/histiocyte-rich large B-cell lymphoma

treated with CAR-T cell therapies or salvage chemotherapy - a single-institution experience. Blood. 2023;142(Supplement 1):6327.
10. Pophali PA, Fein JA, Ahn KW, et al. CD19-directed CART therapy for T-cell/histiocyte-rich large B-cell lymphoma. Blood Adv. 2024;8(20):5290-5296.
11. Bastos-Oreiro M, Iacoboni G, Garcés VN, et al. Chimeric antigen receptor T-cell therapy outcomes in T cell/histiocyte-rich large B-cell lymphoma and subsequent treatment strategies after disease progression: a GELTAMO/GETH study. Hemasphere. 2025;9(2):e70077.
12. Shadman M, Ahn KW, Kaur M, et al. Autologous transplant vs. CAR-T therapy in patients with DLBCL treated while in complete remission. Blood Cancer J. 2024;14(1):1-7.
13. Renders S, Ngoya M, Finel H, et al. Autologous stem cell transplantation in T-cell/histiocyte-rich large B-cell lymphoma: EBMT Lymphoma Working Party study. Blood Adv. 2024;8(21):5571-5578.
14. Dickinson MJ, Carlo-Stella C, Morschhauser F, et al. Glofitamab for relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2022;387(24):2220–2231.
15. Thieblemont C, Karimi YH, Ghesquieres H, et al. Epcoritamab in relapsed/refractory large B-cell lymphoma: 2-year follow-up from the pivotal EPCORE NHL-1 trial. Leukemia. 2024;38(12):2653-2662.