haematologica
Journal of the Ferrata Storti Foundation

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Received: September 25, 2025.
Accepted: March 30, 2026.

Citation: Axel André, Estelle Bourbon, Guillaume Cartron, Franck Morschhauser, Amandine Fayard, Laure Ricard, Roberta Di Blasi, Adrien Chauchet, Stéphanie Guidez, Cristina Castilla-Llorente, Gabriel Brisou, Pierre Bories, Roch Houot, Anne Cuozzo, Elodie Gat, François Lemonnier and Camille Laurent. 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. Haematologica. 2026 Apr 9. doi: 10.3324/haematol.2025.289196 [Epub ahead of print]

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

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Word count (main text): 1500; Number of figure(s): 2; Number of table(s): 1; Supplementary file(s): 1

CONTRIBUTIONS

AA, FL and CL conceived and designed the study; AA wrote the article; ACM performed statistical analysis; CL supervised 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.

DISCLOSURES

A. André: Travel support from Novartis; E. Bourbon: None; G. Cartron: Consulting fees from BMS/Celgene, Roche, Onwards Therapeutics, MabQi; honoraria from Janssen, Takeda, Abbvie, Jansen, Novartis; meeting support from Roche and Janssen; F. Morschhauser: None; A. Fayard: None; L. Ricard: None; R. Di Blasi: Honoraria/advisory roles with Novartis, Kite/Gilead, Janssen, BMS-Celgene, Abbvie; A. Chauchet: None; S. Guidez: None; C. Castilla-Llorente: Honoraria/travel and advisory fees from Gilead/Kite and Nektar Therapeutics; G. Brisou: None; P. Bories: Honoraria/travel support from Abbvie, Astellas, BMS/Celgene, Kite-Gilead, Novartis, Servier; R. Houot: Honoraria from Kite/Gilead, Novartis, BMS/Celgene, Incyte, Janssen, MSD, Takeda, Amgen, Abbvie, and Roche; member on an entity's Board of Directors or advisory committees of Kite/Gilead, Novartis, BMS/Celgene, Tessa Therapeutics, Abbvie and Roche; A. Cuozzo-Minaï: None; E. Gat: None; F. Lemonnier: Honoraria from Takeda and AstraZeneca; advisory roles with Miltenyi, Kyowa Kirin, BMS; travel support from Roche, Gilead, Abbvie, Beigene; research funding from BMS and Roche; C. Laurent: None.

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). Please contact the corresponding author for data requests.

TO THE EDITOR

T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL) is an uncommon variant of diffuse large B-cell lymphoma (DLBCL), typically affecting younger male patients and 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, with some exceeding three 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 (DOR). Response was assessed according to international criteria. Survival estimates were calculated using 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 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 observed in 7 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), 3 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 2 patients and was not investigated in the other 21. All had prior anti-CD20 monoclonal antibody plus chemotherapy; additional treatments included radiotherapy (n=2), IMiDs (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 8 patients. Seventeen patients received bridging therapy, primarily anti-CD20 monoclonal antibody plus chemotherapy (n=12), lenalidomide-based therapy (n=2), immune checkpoint inhibitor (ICI) pembrolizumab (n=2), or radiotherapy plus chemotherapy (n=1). At the time of CAR T-cell infusion, 12 patients had progressive disease (PD), 6 had stable disease or

partial response (SD/PR), and 3 had achieved CR. ECOG at CAR T-cell infusion was preserved (0-1) in 19 patients, LDH 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). Patients' characteristics are summarized in Table 1.

At 3 months post CAR T-cell therapy, among 22 evaluable patients, 14 showed PD, 1 achieved PR and 7 achieved CR, representing an overall response rate of 36% (95% CI 17–59) and a CR rate of 32% (95% CI 14–55). At 12 months, among 21 evaluable patients, CR rate was 19% (95% CI 5-42). Overall, relapse occurred in 16 patients (PET-CT assessed in 8 patients, unknown method in 8 patients), with a median time to relapse of 2.4 months (IQR 1.0–3.1). Among 16 relapsed patients after CAR T-cell therapy, 15 received subsequent therapies and 3 achieved PR or CR. Among R/R patients after CAR T-cell therapy, 7 remained alive after one year, having received lenalidomide and anti-CD20 mAb (n=3), lenalidomide, ibrutinib and anti-CD20 mAb (n=1), ICI and ASCT (n=1), ICI alone (n=1) or a bispecific anti-CD20/CD3 mAb (n=1). Outcome and treatments received for all patients are summarized in Figure 1.

Median follow-up was 22.8 months (95% CI 11.6–37.7), median PFS was 3.1 months (95% CI 2.0–12.0) and median OS was 22.4 months (95% CI 5.0–NA). At 1-year, estimated PFS was 32% (95% CI 14–51) and estimated OS was 63% (95% CI 40–80). Among responders, median DOR was 10.5 months (95% CI 1.4–NA). In patients achieving CR, median duration of CR was 36.2 months (95% CI 1.0–NA). In relapsed patients, no clear benefit was observed with ICI 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 (log-rank p=0.11; Supplementary Figure 1).

During follow-up, 10 patients died: 9 due to disease progression and 1 from unknown cause.

Toxicity was consistent with expectations: 19 patients experienced CAR T-cell specific toxicities, with cytokine release syndrome (CRS) in 18 patients, including 1 case of grade 3–4 CRS, with a median onset of 2.5 days (range 0–8.0). Immune effector cell-associated syndrome (ICANS) occurred in 8 patients, including 2 cases of grade 3–4 ICANS, with median onset of 6.0 days (range 1.0–9.0). Grade 3 infections were reported in 12 patients. No unexpected toxicities or treatment-related deaths occurred.

With 3-month CR rate of 32% and median PFS of 3.1 months, our findings reaffirm 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 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 median duration of CR of 36.2 months. Nevertheless, the limited sample size precluded identification of predictive factors for 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 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 2 of 5 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 ICI 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 evident benefit of ICI despite PD1 expression by T-cells of tumor microenvironment in 5 among 6 patients receiving ICI. Interestingly, among the 7 patients surviving at 1-year after CAR T-cell relapse, 4 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.

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 chemo-sensitive 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 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 investigation 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 ICI, alone or in combination - will be essential to improve outcomes in this rare, challenging disease.

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Table 1: patient characteristics at baseline and at time of CAR T-cell infusion*

	N = 23	%
Sex Male	20	(87%)
Age (years) at 1st infusion of CAR T-cell (median [min ; max])	49	(25 ; 76)
18-64	18	(78%)
65-75	4	(17%)
> 75	1	(4%)
aaIPI 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	(91%)
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° or prior lines of therapy before 1st infusion of CAR T-cell (median [min ; max])	2	(1 ; 10)
1	3	(13%)
2	12	(52%)
≥ 3	8	(35%)
Prior autologous transplant before 1st infusion of CAR T-cell		
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 infusion of CAR T-cell		
No	6	(26%)
Yes†	17	(74%)
Disease status after bridging therapy before 1st infusion of CAR T-cell		
Complete Response	3	(18%)
Partial Response	5	(29%)
Stable Disease	1	(6%)
Progressive Disease	6	(35%)
Not Evaluated	2	(12%)

**The abbreviation CAR T-cell denotes chimeric antigen receptor T-cell), THRLBCL T-cell/histiocyte-rich large B-cell lymphoma, HCT-CI hematopoietic cell transplantation - specific comorbidity index.*

†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.

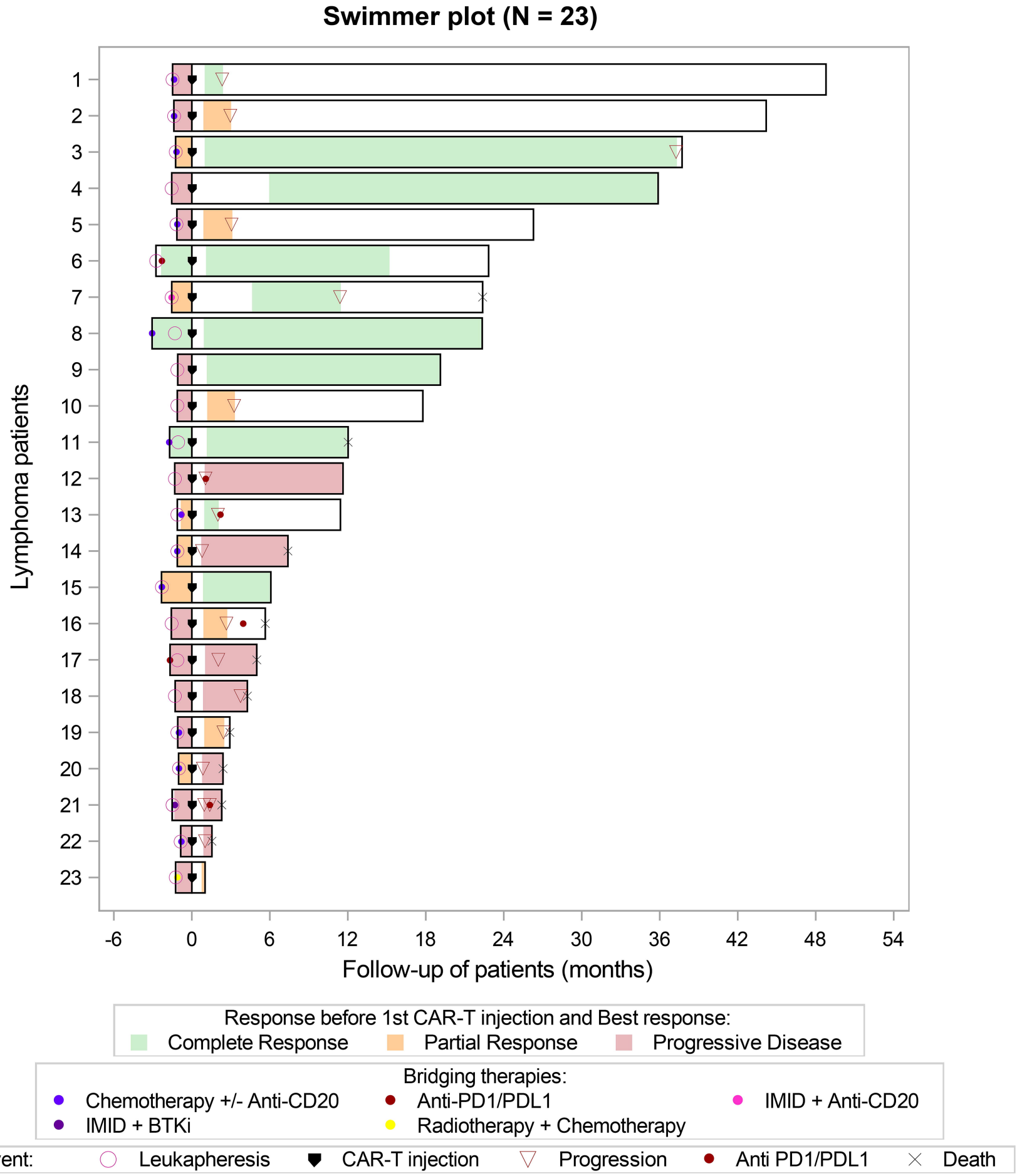
FIGURE LEGENDS

Figure 1. Swimmer-plot depiction of treatment sequence, disease course, and survival in all 23 patients.

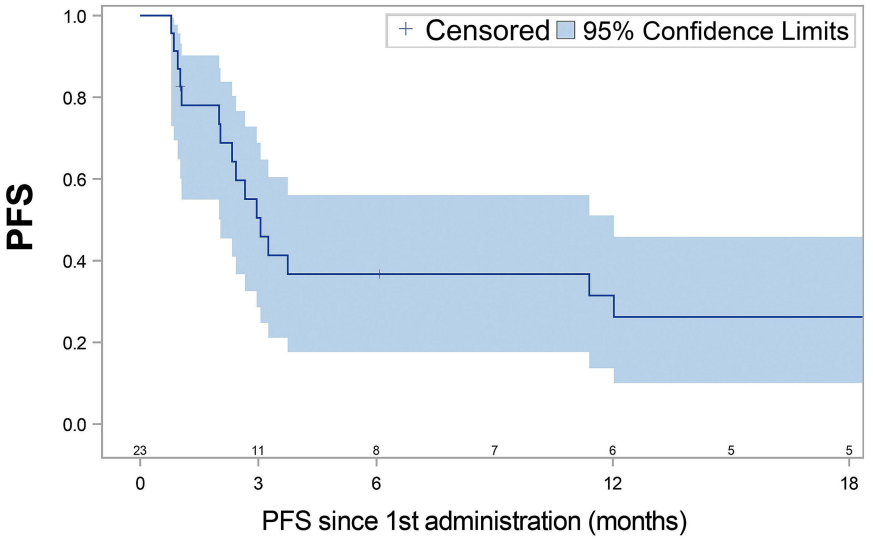
CAR T-cell: chimeric antigen receptor T-cell), IMID: immunomodulatory drug (here the only IMID used was lenalidomide), BTKi: Bruton's Tyrosine Kinase inhibitor (here the only BTKi used was ibrutinib).

Figure 2. Survival outcomes and impact of anti-PD1/PDL1 treatment at relapse after CAR T-cell therapy in THRLBCL.

Kaplan–Meier estimates of progression-free survival (PFS) and overall survival (OS) after 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.

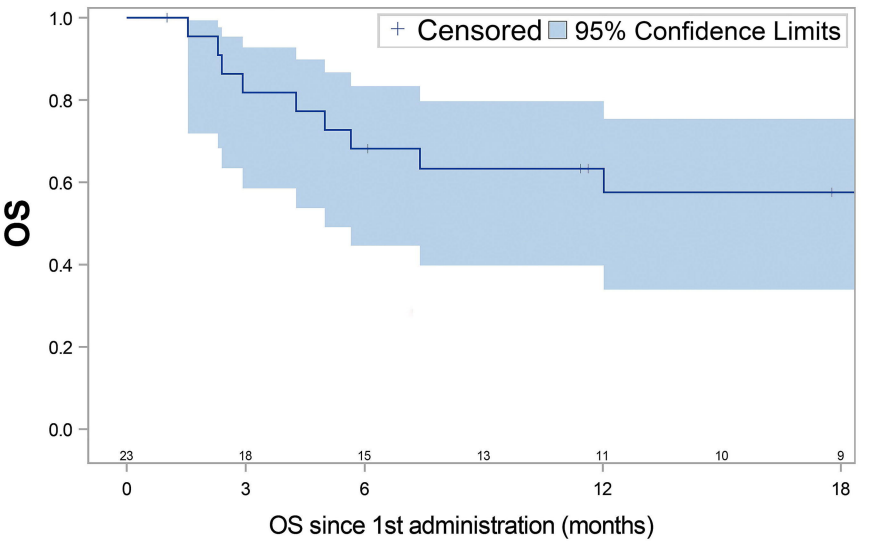

Swimmer plot (N = 23)
Lymphoma patients
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
-6
0
6
12
18
24
30
36
42
48
54
Follow-up of patients (months)
Response before 1st CAR-T injection and Best response:
Complete Response
Partial Response
Progressive Disease
Bridging therapies:
Chemotherapy +/- Anti-CD20
Anti-PD1/PDL1
IMID + Anti-CD20
IMID + BTKi
Radiotherapy + Chemotherapy
Event:
Leukapheresis
CAR-T injection
Progression
Anti PD1/PDL1
Death

A



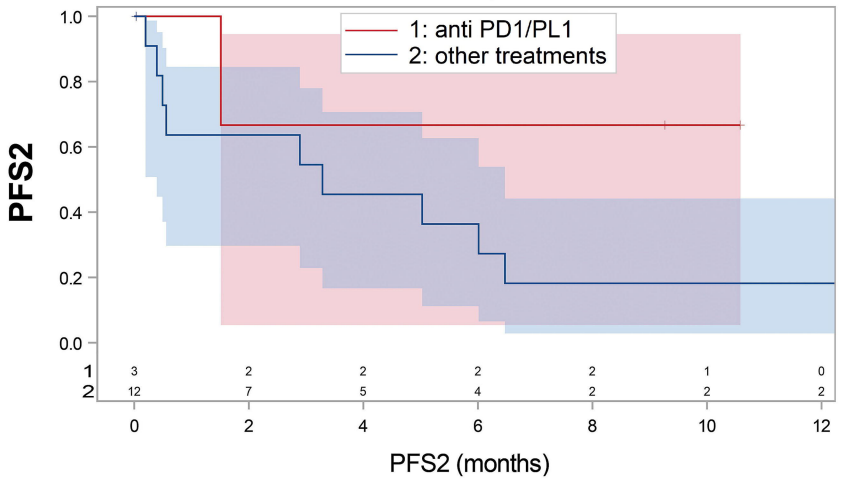
No. of subjects	Event	Censored	Median survival (95% CI)
23	73.9 % (17)	26.1 % (6)	3.1 (2.0 ; 12.0)

B



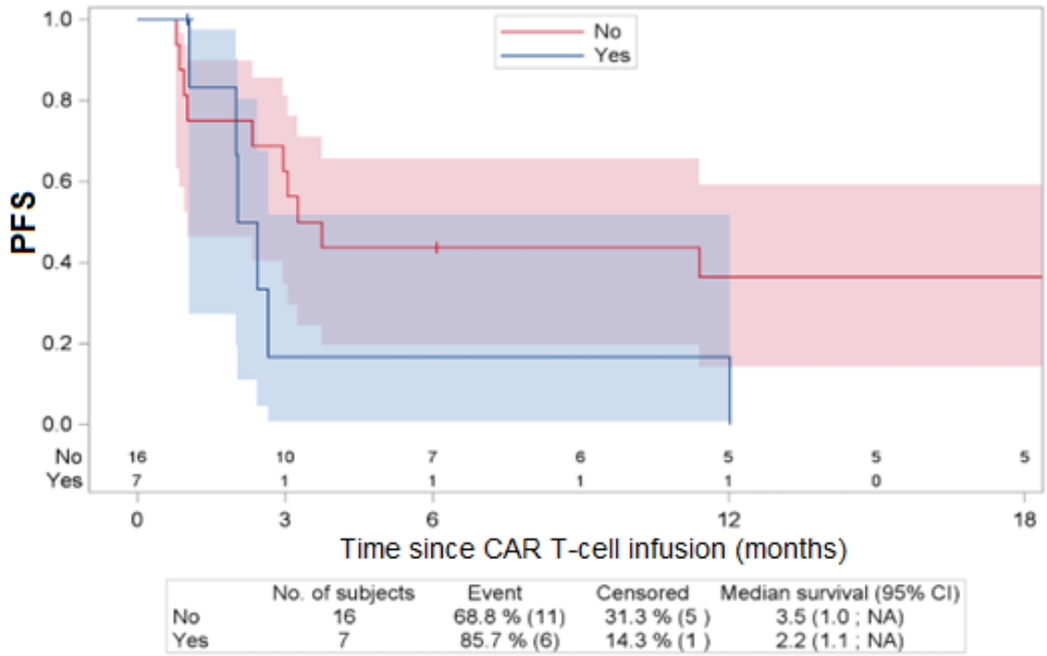
No. of subjects	Event	Censored	Median survival (95% CI)
23	43.5 % (10)	56.5 % (13)	22.4 (5.0 ; NA)

C



	No. of subjects	Event	Censored	Median survival (95% CI)
Anti-PD1/PDL1	3	33.3 % (1)	66.7 % (2)	Not reached (1.5 ; NA)
Others treatments	12	83.3 % (10)	16.7 % (2)	3.3 (0.4 ; 6.5)

Supplementary Figure 1. Impact of an associated low-grade lymphoma on survival after CAR T-cell therapy in THRLBCL.



	No. of subjects	Event	Censored	Median survival (95% CI)
No	16	68.8 % (11)	31.3 % (5)	3.5 (1.0 ; NA)
Yes	7	85.7 % (6)	14.3 % (1)	2.2 (1.1 ; NA)

Supplementary Figure 1. Kaplan–Meier estimates of progression-free survival (PFS) after CAR T-cell therapy according to the presence ("Yes" blue curve, n=7) or absence ("No" red curve, n=16) of an associated low-grade lymphoma (log-rank p=0.11).