RESEARCH ARTICLE

A Multicenter Real-life Prospective Study of Axicabtagene Ciloleucel versus Tisagenlecleucel Toxicity and Outcomes in Large B-cell Lymphomas

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ABSTRACT This real-world prospective observational study across 21 Italian centers (*CART-SIE*) compares axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) outcomes in 485 patients with relapsed/refractory large B-cell lymphoma with baseline characteristics matched by stabilized inverse propensity score weighting. Axi-cel versus tisa-cel had higher all-grade cytokine release syndrome (78.6% vs. 89.3%, $P = 0.0017$) and neurotoxicity (9.9% vs. 32.2%, $P < 0.0001$) but also superior progression-free survival (PFS) at 1 year (46.5% vs. 34.1%, $P = 0.0009$). Even among patients who failed bridging therapy, axi-cel PFS was superior to tisa-cel (37.5% vs. 22.7%, $P = 0.0059$). Differences in overall survival and high-grade immune toxicities were not significant. The CAR-HEMATOTOX score not only predicted hematologic toxicity but also 1-year survival outcomes (51.5% in CAR-HEMATOTOX high vs. 77.2% in CAR-HEMATOTOX low, $P < 0.0001$). Twenty patients developed second primary malignancies, including two cases of T-cell neoplasms. These findings enable more informed selection of anti-CD19 CAR T-cell therapy, balancing bridging, safety, and efficacy considerations for individual patients.

SIGNIFICANCE: The findings of this study on 485 patients with relapsed/refractory large B-cell lymphoma treated with commercial axi-cel and tisa-cel indicate axi-cel's superior PFS after propensity score weighting. The predictive utility of CAR-HEMATOTOX in assessing not only toxicity but also outcomes across both CAR T-cell products may guide future risk-stratified management strategies.

INTRODUCTION

The outcome of refractory large B-cell lymphomas (LBCL) is unsatisfactory following standard chemoimmunotherapy with a median overall survival (OS) of 6 months (1). CD19-targeted chimeric antigen receptor (CAR) T cells have shown notable efficacy and acceptable safety in several hematologic malignancies, including LBCL. Following positive results of pivotal trials, namely, ZUMA-1 (2), JULIET (3), and TRANSCEND (4), axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel), and lisocabtagene maraleucel (liso-cel), CAR T-cell therapies directed against CD19, received the approval for treating relapsed or refractory (R/R) LBCL following at least two prior lines of treatment. More recently, three randomized clinical trials have been conducted on the use of CAR T cells in second-line therapy, namely, ZUMA-7 (5), BELINDA (6), and TRANSFORM (7), two of which had positive outcomes, leading to the approval of axi-cel and liso-cel in second line in several countries.

It is crucial to emphasize that the impressive outcomes from pivotal trials in third-line settings have been replicated by numerous real-world experiences (8–11). Real-world data,

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coupled with the 5-year update from the ZUMA-1 (12) and JULIET (13) trials, increasingly suggest a robust trend wherein approximately 40% of patients may be cured.

Significant efforts have been made in recent years to identify variables that impact the efficacy and toxicity of CAR T-cell therapy. The number of prior treatment lines, disease refractoriness, response to bridging therapy, lactate dehydrogenase (LDH) levels, and inflammatory status at infusion are some of the identified parameters (14–17). However, much of the abovementioned evidence has been collected retrospectively and is still not fully able to explain and predict the different outcomes observed at the individual patient level. With regard to toxicity, clinicians have developed the CAR-HEMATOTOX score, a predictive model incorporating markers of hematopoietic reserve and baseline inflammation, which provides accurate risk assessment for delayed cytopenia in patients undergoing CAR T-cell therapy (18).

Real-world data agree in attributing higher toxicity to axi-cel compared with tisa-cel [any-grade cytokine release syndrome (CRS) ranges, 81%–88% in axi-cel vs. 39%–73% in tisa-cel; any-grade immune effector cell–associated neurotoxicity syndrome (ICANS) ranges, 42%–56% in axi-cel vs. 11%–22% in tisa-cel; refs. 8–11]. However, the efficacy and outcomes of axi-cel and tisa-cel in real-world studies were heterogeneous. Some authors report higher efficacy of axi-cel over tisa-cel [1-year progression-free survival (PFS) 35% vs. 24%, $P = 0.015$ (11)], whereas other datasets, such as those from Spain (10), the United Kingdom (9), and the United States(8), do not show superior efficacy of axi-cel over tisa-cel. Nevertheless, the retrospective nature of these real-world experiences could result in the generation of a number of confounding factors that limit the assessment of treatment causal effect and make them susceptible to selection bias, affecting the true comparison between axi-cel and tisa-cel.

It is now well recognized that the use of propensity score (PS) methods for removing the confounding effects when estimating treatment outcomes, thus generating comparable patient groups that simulate, to the greatest possible extent, a randomized study. Once the PS has been estimated, it can be used in four ways: (i) matching the patients in treatment and control arms using their PSs, (ii) performing PS-stratified analyses, (iii) using PS in multivariable models to adjust the treatment effect, and (iv) applying to apply to each patient an inverse probability of treatment weighting (IPTW; refs. 19, 20).

Despite potential biases associated with this statistical method (21), PS has allowed comparisons between axi-cel and tisa-cel in both pivotal trial data (22) and real-world studies (23). Specifically, in the real-world setting, in the French DESCAR-T registry, Bachy and colleagues (23) have used both matching and IPTW, demonstrating greater efficacy of axi-cel than tisa-cel in terms of overall response rate (ORR; 80% vs. 66%, $P < 0.001$), complete response rate (CRR; 60% vs. 42%, $P < 0.001$), PFS (1-year PFS 46.6% vs. 33.2%, $P = 0.0003$), and OS (1-year OS 63.5% vs. 48.8%), albeit with increased toxicity in terms of CRS (any grade CRS 86.1% vs. 75.6%, $P = 0.006$) and ICANS (any grade 48.8% vs. 22%, $P < 0.001$; ref. 23).

Since November 2019, the Italian Society of Hematology (Società Italiana di Ematologia–SIE) is conducting a prospective multicenter observational study (CART-SIE) to evaluate the efficacy and toxicity of CD19-directed CAR-T in lymphomas.

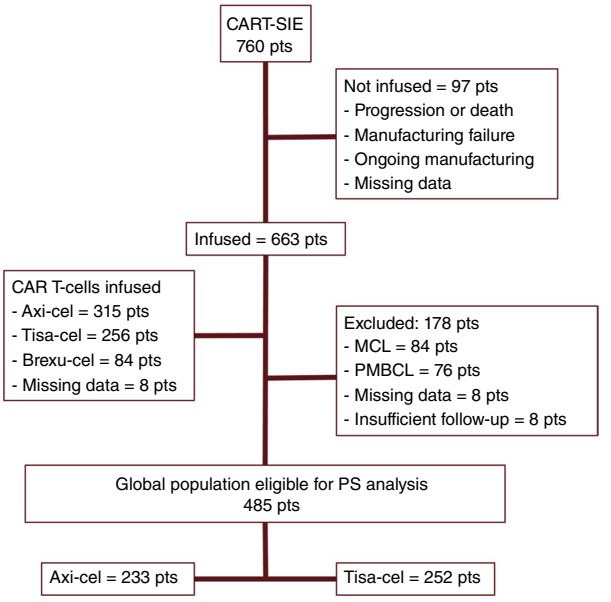

Figure 1. Patient flow diagram. MCL, mantle cell lymphoma; PMBCL, primary mediastinal B-cell lymphoma; pts, patients.

Given the crucial importance of an axi-cel versus tisa-cel comparison to inform clinicians' decision-making, we conducted the largest IPTW comparison among patients with LBCL enrolled in the CART-SIE database.

The CAR-HEMATOTOX score was developed after the start of CART-SIE. Given the emerging significance of hematologic toxicity (18, 24, 25), particularly in light of nonrelapse mortality (NRM) primarily driven by infections (11, 26) a *post hoc* analysis was conducted to validate the CAR-HEMATOTOX in our cohort of patients.

RESULTS

Patient Characteristics

Since November 2019 to December 2023, a total of 760 consecutive patients with R/R B-cell lymphomas treated with commercial axi-cel and tisa-cel after at least two lines of therapy in 20 Italian centers were enrolled in the national CART-SIE database. Following the exclusion of 275 patients [97 not infused, 84 affected by mantle cell lymphoma, 76 affected by primary mediastinal lymphoma (27), 10 due to missing data (not evaluable for response), and 8 with insufficient follow-up], an analysis comparing axi-cel and tisa-cel was conducted on a population of 485 patients with LBCL (Fig. 1).

The patient characteristics are presented in Table 1. In this population, 37% ($n = 177$) of the patients were female, and the median age was 60 years. With regard to the histology, 342 (70.5%) patients were affected by diffuse large B-cell lymphoma (DLBCL; among those with DLBCL, 53.5% were DLBCL not otherwise specified, 20.8% were DLBCL double expressor lymphoma, and 25.7% were DLBCL transformed from indolent lymphoma), whereas the remaining 143 (29.5%) had high-grade B-cell lymphoma (HGBL). Most patients were refractory to the previous treatment line (68%, $n = 330$) and had an advanced stage (72.2%, $n = 350$).

Table 1. Patient characteristics.

	Overall (485 pts)	Tisa (252 pts)	Axi (233 pts)	*P* value*
Sex				0.2196
Female	177 (36.5%)	99 (39.3%)	78 (33.5%)	
Male	307 (63.3%)	153 (60.7%)	154 (66.1%)	
Missing	1 (0.2%)	0 (0%)	1 (0.4%)	
Age				0.0839
Mean (SD)	57.8 (11.4)	58.7 (10.7)	56.7 (12.1)	
Median [Q1, Q3]	60.0 [52.0, 66.0]	61.0 [52.8, 67.0]	59.0 [51.0, 65.0]	
Histology				0.1958
DLBCL	342 (70.5%)	171 (67.9%)	171 (73.4%)	
Double expressor lymphoma	71 (20.8%)	30 (17.5%)	41 (24.0%)	
Indolent transformed	88 (25.7%)	48 (28.1%)	40 (23.4%)	
Not specified	183 (53.5%)	93 (54.4%)	90 (52.6%)	
HGBL	143 (29.5%)	81 (32.1%)	62 (26.6%)	
Double and triple hits	48 (33.6%)	27 (33.3%)	21 (33.9%)	
Not specified	95 (66.4%)	54 (66.7%)	41 (66.1%)	
Disease status				0.0583
Refractory	330 (68.0%)	161 (63.9%)	169 (72.5%)	
Relapse	144 (29.7%)	84 (33.3%)	60 (25.8%)	
Missing	11 (2.3%)	7 (2.8%)	4 (1.7%)	
Ann Arbor				0.1843
I–II	132 (27.2%)	62 (24.6%)	70 (30.0%)	
III–IV	350 (72.2%)	189 (75.0%)	161 (69.1%)	
Missing	3 (0.6%)	1 (0.4%)	2 (0.9%)	
IPI				0.4003
<3	265 (54.6%)	133 (52.8%)	132 (56.7%)	
≥3	202 (41.6%)	110 (43.7%)	92 (39.5%)	
Missing	18 (3.7%)	9 (3.6%)	9 (3.9%)	
Extranodal disease				0.2672
No	206 (42.5%)	113 (44.8%)	93 (39.9%)	
Yes	271 (55.99%)	134 (53.2%)	137 (58.8%)	
Missing	8 (1.6%)	5 (2.0%)	3 (1.3%)	
Extranodal sites ≥2				0.0573
<2	361 (74.4%)	194 (77.0%)	167 (71.7%)	
≥2	103 (21.2%)	44 (17.5%)	59 (25.3%)	
Missing	21 (4.3%)	14 (5.6%)	7 (3.0%)	
Bulky disease				0.1023
No	317 (65.4%)	174 (69.0%)	143 (61.4%)	
Yes	165 (34.0%)	77 (30.6%)	88 (37.8%)	
Missing	3 (0.6%)	1 (0.4%)	2 (0.9%)	
LDH @ infusion				0.1651
Mean (SD)	330 (431)	323 (310)	338 (532)	
Median [Q1, Q3]	214 [173, 330]	224 [176, 344]	206 [169, 311]	
Missing	21 (4.3%)	12 (4.8%)	9 (3.9%)	
CRP @ infusion				0.1115
Mean (SD)	26.6 (46.1)	27.9 (41.5)	25.2 (50.8)	
Median [Q1, Q3]	9.00 [4.00, 28.0]	10.5 [4.00, 32.8]	8.00 [4.00, 20.5]	
Missing	24 (4.9%)	10 (4.0%)	14 (6.0%)	
Ferritin @ infusion				0.6898
Mean (SD)	853 (1,220)	850 (1,190)	856 (1,250)	
Median [Q1, Q3]	421 [221, 971]	408 [190, 1,060]	431 [235, 916]	
Missing	89 (18.4%)	44 (17.5%)	45 (19.3%)	

(*continued*)

Table 1. Patient characteristics. (*continued*)

	Overall (485 pts)	Tisa (252 pts)	Axi (233 pts)	*P* value*
Number of previous treatments				0.4889
Mean (SD)	2.47 (0.813)	2.44 (0.779)	2.50 (0.849)	
Median [Q1, Q3]	2.00 [2.00, 3.00]	2.00 [2.00, 3.00]	2.00 [2.00, 3.00]	
Missing	2 (0.4%)	0 (0%)	2 (0.9%)	
Previous ASCT				0.4764
No	347 (71.5%)	175 (69.4%)	172 (73.8%)	
Yes	134 (27.6%)	73 (29.0%)	61 (26.2%)	
Missing	4 (0.8%)	4 (1.6%)	0 (0%)	
Bridging therapy				0.5628
No	92 (19.0%)	45 (17.9%)	47 (20.2%)	
Yes	393 (81.0%)	207 (82.1%)	186 (79.8%)	
Type of bridging therapy[a]				
Chemotherapy	163 (41.5%)	98 (47.3%)	65 (34.9%)	
Radiotherapy	83 (21.1%)	44 (21.3%)	39 (2.10%)	
Steroids	5 (1.3%)	3 (1.4%)	2 (1.1%)	
Combined (chemotherapy + radiotherapy)	17 (4.3%)	10 (4.8%)	7 (3.8%)	
Immunomodulant	29 (7.4%)	12 (5.8%)	17 (9.1%)	
Pola-based	95 (24.2%)	40 (19.3%)	55 (29.6%)	
Response to bridging therapy				0.0826
CR	44 (11.2%)	30 (14.5%)	14 (7.5%)	
PR	82 (20.9%)	38 (18.4%)	44 (23.7%)	
Stable disease	65 (16.5%)	38 (18.4%)	27 (14.5%)	
PD	160 (40.7%)	81 (39.1%)	79 (42.5%)	
Missing	42 (10.7%)	20 (9.6%)	22 (11.8%)	
CAR-HEMATOTOX				0.8978
Low (0–1)	169 (34.8%)	86 (34.1%)	83 (35.6%)	
High (≥2)	94 (19.4%)	49 (19.4%)	45 (19.3%)	
Missing	222 (45.8%)	117 (46.4%)	105 (45.1%)	
Vein to vein time (months)				<0.0001
Mean (SD)	2.04 (1.44)	2.30 (1.69)	1.75 (1.05)	
Median [Q1, Q3]	1.61 [1.35, 2.27]	1.84 [1.45, 2.50]	1.51 [1.25, 1.84]	
Missing	1 (0.2%)	1 (0.4%)	0 (0%)	

*P value resulting from a Kruskal–Wallis test for continuous variables and from the Fisher exact test for categorical variables.
Abbreviations: CRP, C-reactive protein; IPI, International Prognostic Index; pts, patients.
[a]Type of bridging therapy: immunomodulant bridge therapy includes all patients receiving check-point inhibitors or immunomodulatory drugs alone or in combination with other agent after leukapheresis and before CAR T-cell infusion; Pola-based bridge therapy includes all patients receiving polatuzumab alone or in combination with other agents after leukapheresis and before CAR T-cell infusion.

During the manufacturing time, 393 patients (81%) received bridging therapy: 163 patients (41.5%) underwent chemotherapy, 83 (21%) received radiotherapy alone, and 95 (24.2%) received therapy based on the anti-CD79b mAb conjugate polatuzumab vedotin.

For 263 patients (54.2%), it was possible to calculate the CAR-HEMATOTOX score at the time of infusion; 169 patients had a "low" score, whereas 94 had a "high" score.

Efficacy and Outcomes

In the analyzed 485 patients, the best ORR was 67.6%, with a CRR of 53.2%, whereas the ORR at 90 days after CAR T-cell infusion was 44.5%, with a CRR of 37.7%. With regard to raw response rates, axi-cel has proven more effective than tisa-cel, both in terms of best ORR/CR and ORR/CR at 90 days after CAR T-cell infusion [Table 2; best ORR: axi-cel = 74.7% vs. tisa-cel = 61.1%, OR = 0.48 (95% confidence interval (CI), 0.31–0.74), $P = 0.0009$; best CRR: axi-cel = 59.2% vs. tisa-cel = 47.6%, OR = 0.61 (95% CI, 0.42–0.89), $P = 0.0105$; ORR at 90 days: axi-cel = 48.5% vs. tisa-cel = 40.9%, OR = 0.65 (95% CI, 0.44–0.96), $P = 0.0284$; CRR at 90 days: axi-cel = 41.6% vs. tisa-cel = 34.1%, OR = 0.66 (95% CI, 0.45–0.97), $P = 0.0338$].

With a median follow-up of 13 months (IQR: 6.32–23.55), the median OS for the entire population was 23.5 months (IQR: 7.43–39.51) with a 1-year OS of 65% (95% CI, 60%–70%), whereas the median PFS was 5.1 months (IQR: 2.04–39.51) with a 1-year PFS of 40% (95% CI, 35.3%–44.8%; Supplementary Fig. S1).

Table 2. Efficacy and safety.

	Overall (485 pts)	Tisa-cel (252 pts)	Axi-cel (233 pts)	*OR Tisa vs. Axi* (95% CI)	*P* value*
Best CRR	67.6%	61.1%	74.7%	0.48 (0.31–0.74)	**0.0009**
Best ORR	53.2%	47.6%	59.2%	0.61 (0.42–0.89)	**0.0105**
CRR at +90	37.7%	34.1%	41.6%	0.66 (0.45–0.97)	**0.0338**
ORR at +90	44.5%	40.9%	48.5%	0.65 (0.44–0.96)	**0.0284**
CRS any grade	83.7%	78.6%	89.3%	0.44 (0.26–0.74)	**0.0017**
ICANS any grade	20.6%	9.9%	32.2%	0.23 (0.14–0.38)	**<0.0001**
CRS G > 2	7.8%	7.1%	8.6%	0.94 (0.48–1.84)	0.8573
ICANS G > 2	6.4%	3.2%	9.9%	1.13 (0.42–3.01)	0.8064
Late ICAHT G > 2	5.4%	4.0%	6.9%	0.56 (0.25–1.27)	0.1663

*P value resulting from univariable logistic models.
Abbreviations: ICAHT, immune effector cell–associated hematotoxicity defined according to the European Hematology Association and the European Society for Blood and Marrow Transplantation consensus as absolute neutrophil count ≤500/μL measured ≥2 timepoints.

The duration of response (DoR) and OS did not differ significantly between axi-cel and tisa-cel [1-year DoR: tisa-cel = 50.5% (95% CI, 42.4%–60.2%) vs. axi-cel = 55.7% (95% CI, 47.7%–65.1%), $P = 0.3981$; 1-year OS: tisa-cel = 60.4% (95% CI, 54%–67.5%) vs. axi-cel = 70.8% (95% CI, 64.1%–87.2%), $P = 0.1709$]. However, PFS was better after axi-cel infusion than tisa-cel [1-year PFS: axi-cel = 46.5% (95% CI, 39.8%–54.2%) vs. tisa-cel = 34.1% (95% CI, 28.5%–40.9%), $P = 0.0006$]. Supplementary Table S1 provides a comprehensive summary of baseline variables associated with ORR at day 90, CRR at day 90, PFS, and OS.

Outcomes after PS Weighting

Stabilized inverse PS weighting is a statistical technique used to adjust for confounding in observational studies. It involves assigning weights to each participant based on the inverse of their estimated PSs, aiming to balance treatment groups and enhance the precision of causal inference. Table 3 presents variables used for the PS model before and after stabilized inverse PS weighting. In particular, after weighting, tisa-cel and axi-cel were uniform for age, sex, histology (DLBCL vs. HGBL), disease status (relapse vs. refractory), Ann Arbor at relapse (I–II vs. III–IV), International Prognostic Index (≥3 vs. <3), extranodal disease (no vs. <2 sites vs. ≥2 sites vs. yes but unknown number of sites), bulky disease (>5 cm for the longest diameter of the largest node or mass), normalized LDH [LDH/upper limit of normal (ULN)] and C-reactive protein at infusion, number of previous treatments, autologous stem cell transplantation (ASCT), bridging therapy (no vs. yes with response vs. yes without response), and time between apheresis and infusion.

After PS weighting, the data suggesting greater activity of axi-cel in terms of PFS were confirmed. Moreover, OS was confirmed as nonsignificantly different between axi-cel and tisa-cel. [Fig. 2A: OS: weighted log-rank test *P* value = 0.1033, HR 1.30 (95% CI, 0.92–1.83), $P = 0.1399$; Fig. 2B: weighted log-rank *P* value = 0.0002, HR = 1.59 (95% CI, 1.21–2.08), $P = 0.0009$].

Toxicity

Toxicities associated with CAR T cells are detailed in Table 2. Any-grade CRS occurred in 78.6% of tisa-cel and 89.3% of axi-cel (OR = 0.44, 95% CI, 0.26–0.74, $P = 0.0017$), with grade ≥3 CRS observed in 7.1% of tisa-cel and 8.6% of axi-cel (OR = 0.94, 95% CI, 0.48–1.84, $P = 0.8573$). Any-grade ICANS occurred in 9.9% of tisa-cel and 32.3% of axi-cel (OR = 0.23, 95% CI, 0.14–0.38, $P < 0.0001$), whereas grade ≥3 ICANS was seen in 3.2% of tisa-cel and 9.9% of axi-cel (OR = 1.13, 95% CI, 0.42–3.01, $P = 0.8064$). Grade ≥2 late immune effector cell–associated hematotoxicity was observed in 4.0% of tisa-cel and 6.9% of axi-cel (OR = 0.56, 95% CI, 0.25–1.27, $P = 0.1663$).

The 1-year NRM was 2.0% (95% CI, 1.0%–3.9%). Most deaths (11/16 = 69%) were infection related, with 3/11 attributed to SARS-CoV2 infection. The NRM did not differ between tisa-cel and axi-cel: among the 16 patients who died from causes other than underlying disease progression, seven received axi-cel and eight received tisa-cel (Fine and Gray HR = 0.83, 95% CI, 0.32–2.14, $P = 0.6949$).

With a median follow-up of 13 months (IQR: 6.32–23.55) from the CAR T-cell infusion, second primary malignancies were documented in 4.1% (20/485) of the patients: 3.6% (9/252) treated with tisa-cel and 4.7% (11/233) with axi-cel (3.6% vs. 4.7%, $P = 0.6490$).

Among these 20 cases of second primary malignancies, second hematologic malignancies occurred in 17 cases (17/20 = 85%), including 13 myelodysplastic syndrome, 1 acute myeloid leukemia, 1 non–Hodgkin lymphoma Epstein–Barr virus related, and 2 T-cell lymphoproliferative diseases (one T-large granular lymphocytes and one T-helper follicular proliferation). Additionally, three patients developed late-onset solid tumors: one Epstein–Barr virus–related nasopharyngeal carcinoma, one colorectal cancer, and one prostatic cancer in a patient with a concurrent benign adenoma. The median age of the 20 patients experiencing late-onset malignancies was 53 years (range, 30–70); the median number of prior treatments was 2 (range, 2–5), with 11 of 20 having undergone previous ASCT (11/20 = 55%); 15 of them developed CRS after CAR-T infusion, and five experienced ICANS. Among the 17 patients who developed second hematologic malignancies, at 3 months after CAR T-cell infusion, 7/17 (41%) were in complete response (CR), 4/17 (23%) were in partial response (PR), 4/17 (23%) were in progressive disease (PD), and 2/17 (12%) were not assessed.

Table 3. Stabilized inverse PS weighting: patient characteristics before and after weighting.

	Before weighting = 485 pts			After weighting = 367.1 pts		
	Tisa-cel *n* = 252	Axi-cel *n* = 233	SMD[a]	Tisa-cel *n* = 184.6	Axi-cel *n* = 182.5	SMD[a]
Age, mean (SD)	58.7 (10.7)	56.7 (12.1)	0.177	57.8 (11.3)	58 (11.3)	0.012
Sex, male	153 (60.7%)	155 (66.5%)	0.121	118 (64%)	117 (64.3%)	0.007
Histology, HGBL	81 (32.1%)	62 (26.6%)	0.122	53.2 (28.8%)	53.6 (29.4%)	0.012
Disease status, relapse (%)	84 (33.3%)	60 (25.8%)	0.167	53.1 (28.8%)	51.6 (28.2%)	0.012
Stage, III–IV	190 (75.4%)	163 (50%)	0.122	133.8 (72.5%)	133.3 (73%)	0.010
IPI ≥3	110 (43.7%)	92 (39.5%)	0.085	75.8 (41.1%)	75.1 (41.1%)	0.002
Extranodal combo			0.223			0.034
<2	81 (32.1%)	74 (31.8%)		62.3 (33.7%)	60.7 (33.3%)	
≥2	44 (17.5%)	59 (25.3%)		40.6 (22.0%)	39.1 (21.4%)	
No	118 (46.8%)	96 (41.2%)		77.1 (41.8%)	78.7 (43.1%)	
Missing	9 (3.6%)	4 (1.7%)		4.7 (2.5%)	4 (2.2%)	
Bulky disease	77 (30.6%)	88 (37.8%)	0.153	62 (33.6%)	62.4 (34.2%)	0.012
Normalized LDH (LDH/ULN), mean (SD)	21.14 (51.15)	1.13 (1.27)	0.009	1.16 (1.20)	1.14 (1.28)	0.009
CRP, mean (SD)	27.14 (40.79)	24.18 (49.4)	0.065	26.97 (39.76)	26.76 (54.57)	0.004
N° prev. treatment, mean (SD)	2.44 (0.78)	2.5 (0.85)	0.071	2.47 (0.8)	2.46 (0.81)	0.019
Previous ASCT	73 (29%)	61 (26.2%)	0.062	48.8 (26.4%)	48.6 (26.6%)	0.004
Bridging response			0.067			0.010
No bridge	45 (17.9%)	47 (20.2%)		32.2 (17.5%)	31.3 (17.2%)	
No response	139 (55.2%)	128 (54.9%)		105 (57.5%)	105.3 (57.1%)	
Response	68 (27%)	58 (24.9%)		47 (25.5%)	46.3 (25.3%)	
Vein to vein time mean (SD)	2.3 (1.68)	1.75 (1.05)	0.396	1.89 (0.78)	1.84 (1.16)	0.051

Abbreviation: pts, patients.
[a]SMD, standardized mean difference: assesses the balance in covariates between treatment groups, with a lower value indicating improved equivalence and reduced bias.

Six of the 17 patients (35%) were CAR-HEMATOTOX high, 5/17 (30%) were CAR-HEMATOTOX low, and 6/17 (35%) were not assessed.

The Role of Bridging Therapy

The 1-year OS rates for patients (i) not undergoing bridging, (ii) with bridging failure, (iii) PR to bridging, and (iv) CR after bridging were 77%, 54%, 68%, and 82%, respectively ($P < 0.0001$, as shown in Fig. 3A). Correspondingly, the 1-year PFS rates for patients (i) not undergoing bridging, (ii) with bridging failure, (iii) PR to bridging, and (iv) CR after bridging were 47%, 29%, 40%, and 72%, respectively ($P < 0.0001$; Fig. 3B).

In patients who experienced bridging therapy failure (stable disease or PD after bridging therapy), the 1-year PFS was 22.7% with tisa-cel and 37.5% with axi-cel ($P = 0.0059$; Fig. 3C), whereas the 1-year OS was 48.4% with tisa-cel and 61.8% with axi-cel ($P = 0.1844$; Supplementary Fig. S2).

Patients who received a bridging therapy based on polatuzumab-vedotin (pola) demonstrated significantly improved PFS compared with those receiving other types of therapies (Fig. 3D: 1-year PFS = 47.6% for pola-based vs. 35.5% for non–pola-based, $P = 0.0340$).

We did not observe a statistically significant difference in terms of PFS in patients receiving bridging therapy versus patients not receiving bridging therapy (Supplementary Fig. S3: 1-year PFS 44% vs. 35%, $P = 0.1584$).

CAR-HEMATOTOX Score Predicted Toxicity and Survival

In our study, the CAR-HEMATOTOX score demonstrated its efficacy in predicting hematologic toxicity. Specifically, the incidence of severe (G ≥ 2) late immune effector cell–associated hematotoxicity was 9.6% in those with high CAR-HEMATOTOX and 1.8% in those with low CAR-HEMATOTOX (OR = 7.24, 95% CI, 1.9–27.62, $P = 0.0038$).

Additionally, severe CRS (G ≥ 3) occurred in 12.8% of patients with high CAR-HEMATOTOX compared with 3% in those with low CAR-HEMATOTOX (OR = 4.52, 95% CI, 1.53–13.36, $P = 0.0063$), and any-grade ICANS was 33% in high CAR-HEMATOTOX versus 12.4% in low CAR-HEMATOTOX (OR = 3.47, 95% CI, 1.85–6.5, $P = 0.0001$).

Notably, patients with a low CAR-HEMATOTOX score at CAR T-cell infusion demonstrated improved OS and PFS compared with those with a high CAR-HEMATOTOX score (Fig. 4A: 1-year OS: 51.7% in CAR-HEMATOTOX high vs. 77.2% in CAR-HEMATOTOX low, $P < 0.0001$; Fig. 4B: 1-year PFS: 29% in CAR-HEMATOTOX high vs. 43.6% in CAR-HEMATOTOX low, $P = 0.0003$).

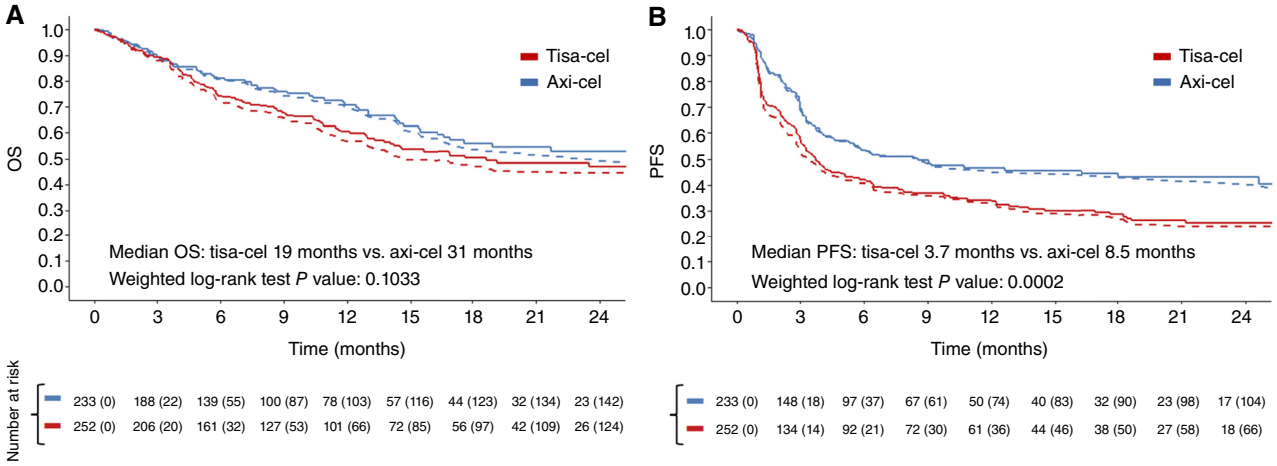

Figure 2. Survival from infusion of tisa-cel vs. axi-cel before (continuous line) and after (dotted lines) PS weighting. **A,** OS. **B,** PFS.

In order to evaluate whether CAR-HEMATOTOX was associated with the outcome within each CAR T-cell product, a bivariable Cox model with interaction was estimated (Supplementary Table S2). In terms of PFS, the interaction *P* value was 0.9963, and the HRs of the score were similar among the two products [in tisa-cel HEMATOTOX high vs. low HR = 1.79 (95% CI, 1.12–2.85); in axi-cel HEMATOTOX high vs. low HR = 1.78 (95% CI, 1.17–2.72)], consistent with the fact that the effect of CAR-HEMATOTOX validity does not vary among the two CAR T-cell products.

DISCUSSION

The current prospective study including 485 patients with R/R LBCL treated with commercially available axi-cel and tisa-cel reaffirms pivotal trial outcomes and real-world data with some novel findings. Notably, our study reflects findings observed in real-world investigations conducted in Europe and the United States, as summarized in Supplementary Table S3, with a 1-year PFS of 40%, 1-year OS of 65%, ORR/CRR at 90 days 44/38%, respectively, and an incidence of any-grade CRS and ICANS of 84% and 21%, respectively.

In a scenario in which conducting randomized trials is impossible and comparing clinical trials is not only inappropriate but also impossible due to the different designs of the trials themselves, both in third-line (2–4) and second-line settings (5–7), real-world studies can assume crucial significance in helping clinical decisions (28). PS methods like matching and IPTW, both utilized by Bachy and colleagues (23) to analyze data from DESCAR-T registry, directly address selection bias, ensuring tighter control of baseline covariates. Primarily, PS serves as a direct tool to eliminate selection bias inherent in a study, forging treatment and control cohorts characterized by comparable baseline features. IPTW, in particular, allows estimation of the average treatment effect; in this study, average treatment effect for tisa-cel versus axi-cel would represent the difference in the average outcomes if everyone in the population received tisa-cel versus if everyone received axi-cel. Thus, IPTW allows mimicking a clinical trial randomly assigning patients to axi-cel and tisa-cel, enhancing result interpretation within the same study, and offering robust and reliable comparisons between the two treatments. Furthermore, IPTW exhibits flexibility in managing missing data, contingent upon the presence of covariates within the study milieu (19). This versatility enhances the applicability and robustness of IPTW in addressing confounding factors and refining the validity of observational research findings (19, 20).

Our study, the largest prospective observational trial with PS, validates previous findings by Bachy and colleagues (23), highlighting axi-cel's superior efficacy compared with tisa-cel in terms of ORR [48% vs. 41%, $P = 0.03$), CRR (42% vs. 34%, $P = 0.03$), and PFS (1-year PFS: 46% vs. 34%, $P = 0.0002$; Supplementary Table S3]. However, the lack of a significant difference in OS highlights the promising impact of emerging treatment strategies, such as bispecific antibodies (29), in patients refractory or relapsed after CAR T-cell therapy (30) and suggests that the selection of a specific CAR T-cell therapy should also take into consideration factors beyond efficacy alone, such as age, comorbidities, and concerns about toxicities.

Axi-cel had an increased toxicity, particularly in terms of CRS and ICANS rates. Of interest, although trends indicate higher hematologic toxicity with axi-cel, it is noteworthy that this does not translate into a significantly higher NRM, with an incidence of 2% at 1 year, predominantly driven by infection-related causes in both CAR T-cell products.

The occurrence of secondary primary malignancies in CAR T cell–treated patients is raising significant concerns (31). In our cohort, with a median follow-up of 13 months, we documented 20 cases of secondary malignancies, accounting for 4.1% of the 485 infused patients. Given the rarity of this event within a heavily pretreated population and the relatively short follow-up, establishing a causal relationship between CAR T-cell therapy and the development of secondary malignancies was not feasible and warrants further investigation.

Previous studies have already suggested that the response to bridging therapy is a significant determinant of the outcome achieved by CAR T-cell treatment (11, 32). Our study

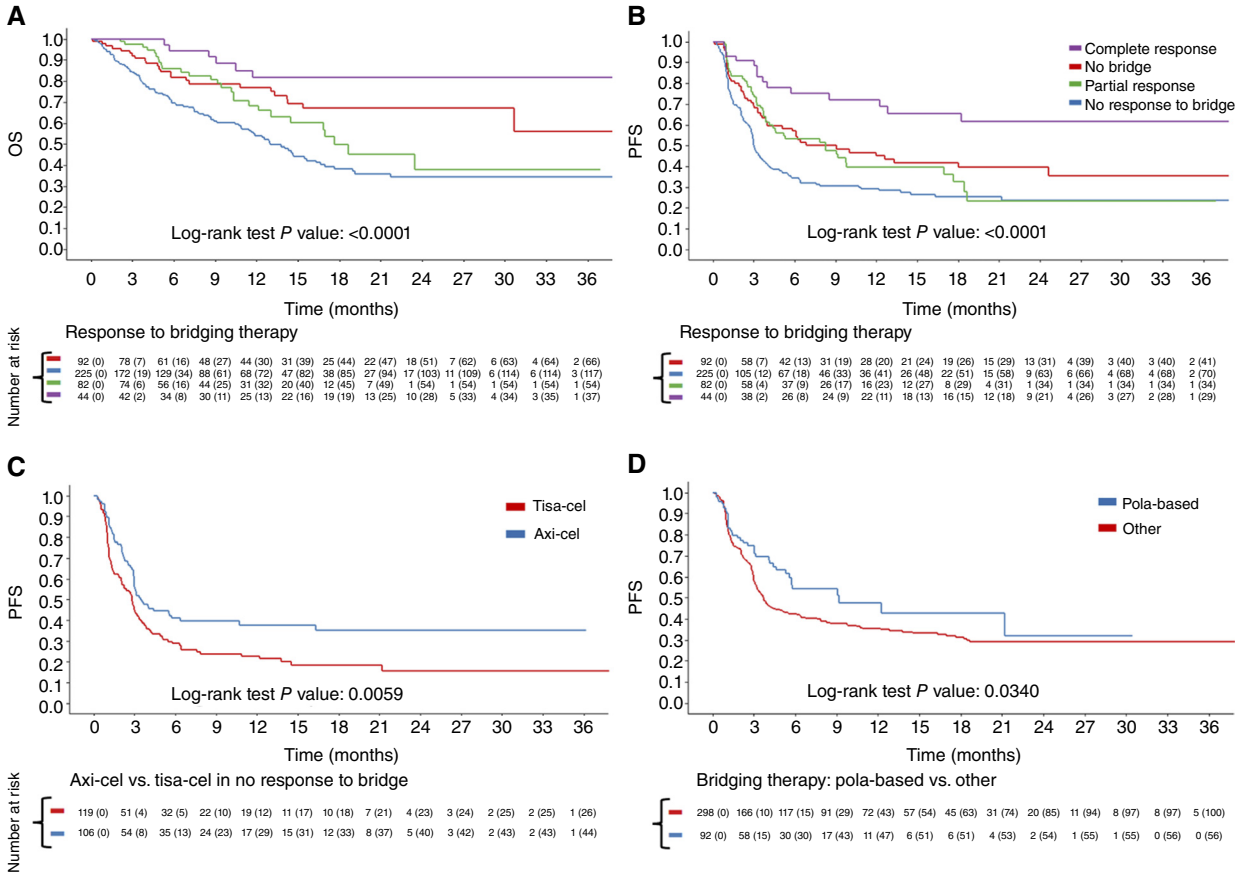

Figure 3. Survival according to response to bridging therapy. **A,** OS according to response to bridging therapy. **B,** PFS according to response to bridging therapy. **C,** PFS axi-cel vs. tisa-cel in patients not responding to bridge therapy. **D,** PFS in patients receiving pola-based bridging therapy vs. other type of bridging therapy.

emphasizes the critical role of bridging therapy (12-month OS: no bridging/bridging failure/PR and CR after bridging were 77%/54%/68% and 82%, respectively, $P < 0.0001$) and additionally highlights the better PFS observed with axi-cel than tisa-cel in patients who did not respond to bridging therapy (37.5% vs. 22.7%, $P = 0.0059$), providing a valuable insight for decision-making. In any case, these data do not definitively show if debulking with bridge therapy before CAR-T leads to better outcomes or if responding to bridge therapy is just a surrogate of more favorable disease that might naturally respond more to CAR T cells.

In the context of a population predominantly refractory to previous treatment lines, it is evident that in the choice of the bridging therapy, the focus should shift from standard chemotherapy protocols to new agents such as bispecific antibodies (29, 33, 34), antibody–drug conjugates (35–38), immunomodulatory drugs (39), or antibodies targeting different antigens compared with the anti-CD20 agents (40). In this scenario, our study highlights that bridging with regimens containing polatuzumab vedotin is associated with better PFS than other strategies (1-year PFS = 47.6% vs. 35.5%, $P = 0.0340$).

A further finding is that the CAR-HEMATOTOX is validated as a simple yet robust tool for predicting hematologic toxicity and outcomes, offering a unique capability to capture the hematopoietic reserve and inflammatory status of each patient before CAR T-cell infusion (18, 41, 42). In contrast to previous reports (42) in which there was a balanced number of patients with high and low scores, in our study, there were twice as many patients with low scores compared with those with high scores. It is possible that the more recent optimization of bridge therapies and the increased awareness among local investigators of the importance of bringing patients to infusion in a less "inflamed" state may have contributed to generating a cohort with lower scores (it should be noted that the score was calculated for 54% of the total patients, largely consisting of those treated more recently). To the best of our knowledge, this is the first time that the predictive capacity of the CAR-HEMATOTOX extends beyond toxicity to forecast outcomes in a prospective study, encompassing PFS and OS (1-year PFS: 29% in CAR-HEMATOTOX high vs. 43.6% in CAR-HEMATOTOX low, $P = 0.0003$; 1-year OS: 51.7% in CAR-HEMATOTOX high vs. 77.2% in CAR-HEMATOTOX low, $P < 0.0001$), thus enhancing the multifaceted nature of risk stratification. Furthermore, it is noteworthy that the CAR-HEMATOTOX interaction model demonstrated predictive capability in both tisa-cel and axi-cel. The score equips clinicians with a simple, unexpensive, and pragmatic approach to customize treatment decisions, leveraging insights from individual patient profiles.

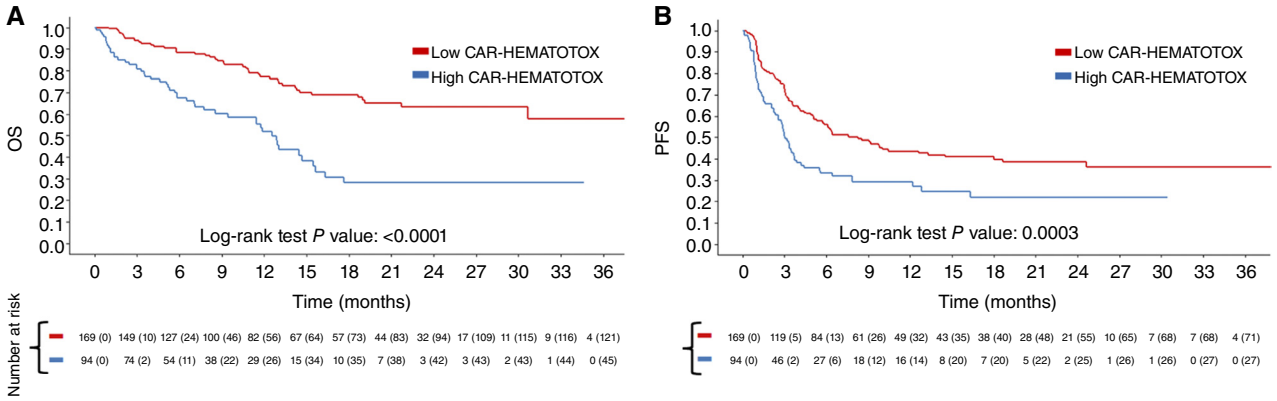

Figure 4. Survival according to the CAR-HEMATOTOX score. **A,** OS. **B,** PFS.

In conclusion, our prospective study indicates that axi-cel is superior to tisa-cel in terms of PFS and should be preferred when patients failing bridging. Furthermore, the CAR-HEMATOTOX score not only anticipates hematologic toxicity but also predicts survival.

METHODS

Study Design

The CART-SIE study is an ongoing multicenter prospective observational study. From August 2019, all patients meeting the eligibility criteria for CAR T-cell therapy, as defined by the "Agenzia Italiana del Farmaco" (Italian drug agency), were consecutively enrolled. Detailed eligibility criteria in accordance with Agenzia Italiana del Farmaco are provided in the Supplementary Materials (Supplementary Table S4).

It is important to highlight that liso-cel was approved in February 2024 in Italy and its reimbursement status is still pending; therefore, it is not included in our study.

Eligible patients included those with R/R aggressive LBCLs, such as DLBCL (not otherwise specified, HGBL and DLBCL arising from transformed follicular lymphoma) and HGBL. A centralized review of histologic specimens was not performed. These patients had undergone at least two prior treatment lines, possessed an Eastern Cooperative Oncology Group performance status of 0 to 1, and were treated with CAR T-cell therapy. The choice between axi-cel and tisa-cel was made by local investigators based on their clinical practice.

The study, coordinated by the "Fondazione IRCCS Istituto Nazionale dei Tumori" in Milan, Italy, is being conducted in collaboration with the SIE across 21 approved Italian hematologic centers, authorized by the regulatory agency for the administration of CAR T-cell therapy (refer to Supplementary Table S5 for a breakdown of patients enrolled by each center).

The study adhered to the Declaration of Helsinki and Good Clinical Practice guidelines, obtaining ethical approval from institutional review boards at each site (INT 180/19, approval number 431/DG, 2019, ClinicalTrials.gov ID: NCT06339255). All patients provided written informed consent. All patients underwent planned lymphodepletion chemotherapy in accordance with the label of each product (Supplementary Table S4).

Endpoint and Assessment

The study aimed to compare the efficacy, outcomes, and toxicity of axi-cel versus tisa-cel. The primary endpoint was investigator-assessed PFS. Secondary endpoints encompassed OS, DoR, ORR, CRR, and safety, specifically the incidence of CRS, ICANS, long-term cytopenia, and NRM. Response was assessed according to the Lugano 2014 criteria (43), with all survival curves calculated from the date of CAR T-cell infusion, unless otherwise specified. The response assessment schedule was established by local investigators based on their clinical practice.

CRS and ICANS were graded according to the American Society for Transplantation and Cellular Therapy consensus (44). Hematologic toxicity was defined and graded based on the consensus grading outlined by the European Hematology Association and the European Society for Blood and Marrow Transplantation (ref. 41).

Statistical Analysis

The assessment of efficacy in the study was conducted through the following methodologies.

PFS. For PFS, time was measured from CAR T-cell infusion to the date of PD or death, whichever occurred first, with censoring at the latest follow-up for patients alive without progression.

OS. For OS, time was measured from the date of CAR T-cell infusion to the date of death from any cause, with censoring at the latest follow-up for living patients.

DoR. For patients in CR or PR, DoR time was measured from the date of achievement of response to the date of progression or death, whichever occurred first, with censoring at the latest follow-up date for patients still alive without progression.

PFS, OS, and DoR curves were estimated using the Kaplan–Meier method. Between-group comparisons of Kaplan–Meier curves were carried out using the log-rank test.

ORR. The percentage of patients exhibiting a response was determined by dividing the sum of CRs and PRs by the total number of evaluable patients at each specific timepoint. Patients not assessable for response, for any reason, were considered nonresponding in the calculations. Additionally, 95% exact binomial CIs for the response percentage were estimated.

Safety evaluations were conducted as follows:

NRM) after CAR T-cell therapy: The interval between CAR T-cell infusion and the date of nonrelapse death was measured, with censoring at the latest follow-up for patients alive without relapse. Cumulative incidence curves for NRM were estimated considering disease recurrence as a competing event. Between-group comparisons were performed using the Gray test.

CRS, ICANS, and hematologic toxicity were summarized employed with descriptive statistics, and between-group comparisons were done using univariable logistic models.

Binary associations between continuous and categorical variables were assessed using the Kruskal–Wallis tests. The Fisher–Freeman–Halton test was used when testing associations between two categorical variables (45). The differences in characteristics between the two treatment groups are expressed in standardized mean differences, which are able to detect treatment unbalances (46). CAR-HEMATOTOX was calculated according to Rejeski and colleagues (18).

PS Matching Procedures

Outcome comparison between the two CAR-T products was done using the stabilized (47) IPTW methodology. Simulating studies (48) showed that the use of stabilized IPTW preserves the sample size close to the original data, thus maintaining an appropriate type I error rate, whereas the not stabilized IPTW tends to reject the null hypothesis of the absence of treatment effect too frequently because of inflated sample size. PS was calculated using a logistic model estimating the probability of being treated with tisa-cel (the largest group). Consistent with an article previously published by Bachy and colleagues (13), several crucial variables were taken into consideration in formulating the PS model: histology, age, gender, disease status (distinguishing between R/R diseases), Ann Arbor stage (categorized as I/II or III/IV), the International Prognostic Index with a differentiation between values less than 3 and those greater than or equal to 3, extranodal disease (no vs. <2 sites vs. ≥2 sites vs. yes but unknown number of sites), LDH levels at infusion with respect to the ULN (LDH/ULN ratio), C-reactive protein levels at infusion, the presence of bulky disease, the number of prior treatments, the previous ASCT, the utilization of bridging therapy (with options ranging from none to yes without response or yes with response), and time between apheresis and infusion.

The number of missing values for each variable was low (<5%), and these were imputed using the median value for the continuous variables and the mode category for the categorical variables in order to minimize data loss.

The comparison of tisa-cel versus axi-cel in survival outcomes was then performed using weighted log-rank test and weighted Cox models.

Data Availability

De-identified data collected in this study are available upon request from the corresponding author.

Authors' Disclosures

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Authors' Contributions

F. Stella: Conceptualization, data curation, formal analysis, investigation, writing–original draft, writing–review and editing. **A. Chiappella:** Data curation, formal analysis, supervision, investigation, writing–review and editing. **B. Casadei:** Data curation, writing–review and editing. **S. Bramanti:** Data curation, writing–review and editing. **S. Ljevar:** Data curation, software, formal analysis, visualization, methodology, writing–review and editing. **P. Chiusolo:** Data curation, investigation, writing–review and editing. **A. Di Rocco:** Data curation, writing–review and editing. **M.C. Tisi:** Data curation, writing–review and editing. **M.G. Carrabba:** Data curation, writing–review and editing. **I. Cutini:** Data curation, writing–review and editing. **M. Martino:** Data curation, writing–review and editing. **A. Dodero:** Data curation, writing–review and editing. **F. Bonifazi:** Data curation, writing–review and editing. **A. Santoro:** Data curation, writing–review and editing. **F. Sorà:** Data curation, writing–review and editing. **B. Botto:** Data curation, writing–review and editing. **A.M. Barbui:** Data curation, writing–review and editing. **D. Russo:** Data curation, writing–review and editing. **M. Musso:** Data curation, writing–review and editing. **G. Grillo:** Data curation, writing–review and editing. **M. Krampera:** Data curation, writing–review and editing. **J. Olivieri:** Data curation, writing–review and editing. **M. Ladetto:** Data curation, writing–review and editing. **F. Cavallo:** Data curation, writing–review and editing. **M. Massaia:** Data curation, writing–review and editing. **L. Arcaini:** Data curation, writing–review and editing. **M. Pennisi:** Data curation, writing–review and editing. **P.L. Zinzani:** Data curation, writing–review and editing. **R. Miceli:** Conceptualization, data curation, software, formal analysis, supervision, visualization, methodology, writing–review and editing. **P. Corradini:** Conceptualization, resources, data curation, supervision, funding acquisition, investigation, writing–original draft, project administration, writing–review and editing.

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Note

Supplementary data for this article are available at Blood Cancer Discovery Online (https://bloodcancerdiscov.aacrjournals.org/).

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