Real-world comparison of lisocabtagene maraleucel and axicabtagene ciloleucel in large B-cell lymphoma: an inverse probability of treatment weighting analysis with 3-year follow-up

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Abstract

Lisocabtagene maraleucel (liso-cel) and axicabtagene ciloleucel (axi-cel) are Food and Drug Administration- and European Medicines Agency-approved chimeric antigen receptor (CAR) T-cell therapies for relapsed/refractory large B-cell lymphoma (LBCL). However, comparative real-world analyses of their efficacy and toxicity with extended follow-up are lacking. We conducted a retrospective study of 160 LBCL patients treated at the Fred Hutchinson Cancer Center with commercial liso-cel or axi-cel per standard of care. Using inverse probability of treatment weighting (IPTW) to mitigate treatment allocation bias and multivariable adjustments to minimize other sources of confounding, we assessed the impact of CAR T-cell product type on outcomes. Axi-cel was associated with significantly higher rates of cytokine release syndrome (CRS; grade [G]1+: adjusted odds ratio [aOR] =4.27; *P*=0.004; G2+: aOR=2.88; *P*=0.006), immune effector cell-associated neurotoxicity syndrome (ICANS; G1+: aOR=2.10; *P*=0.048), and immune effector cell-associated hematotoxicity (ICAHT; G1+: aOR=8.09; *P*<0.001; G2+: aOR=3.86; *P*=0.001). Axi-cel was also associated with more frequent use of supportive care measures, such as tocilizumab (aOR=2.50; *P*=0.017), dexamethasone (aOR=2.77; *P*=0.007), and cefepime (aOR=3.37; *P*=0.001). We could not confirm statistically significant differences in the response rates and survival outcomes after liso-cel *versus* axi-cel (complete response: aOR=1.12; *P*=0.8; overall survival: adjusted hazard ratio [aHR] =1.34; *P*=0.3; progression-free survival: aHR=0.97; *P*=0.9; duration of response: aHR=0.89; *P*=0.7; cumulative incidence of relapse: aHR=0.92; *P*=0.8). In summary, although axi-cel was associated with greater toxicity requiring more intensive management, the response rates and survival outcomes were comparable between axi-cel and liso-cel.

Introduction

CD19 chimeric antigen receptor (CAR) T-cell therapy has transformed the management of relapsed/refractory (R/R) large B-cell lymphoma (LBCL), offering the potential to cure 30-40% of treated patients.[1] Currently approved products include axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel), and lisocabtagene maraleucel (liso-cel). Axi-cel and liso-cel are approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as second-line treatments for high-risk LBCL patients with primary refractory disease or relapse/progression within 12 months, having demonstrated superiority over standard-of-care (SOC) therapy.[2-9] In contrast, the BELINDA study did not confirm a similar benefit for tisa-cel in this setting.[10] Retrospective adjusted comparisons have revealed differences in efficacy and toxicity profiles among these therapies. Axi-cel showed superior anti-tumor activity compared to tisa-cel, albeit with greater toxicity.[11,12] The TRANSCEND NHL 001 trial, which led to the initial approval of liso-cel, indicated a more favorable toxicity profile, a finding which was re-demonstrated in a non-transplant eligible population.[13-15] A matching-adjusted indirect treatment comparison (MAIC) suggested comparable efficacy between liso-cel and axi-cel, with a better safety profile for liso-cel. However, the analysis was restricted to clinical trial patients, who

generally have better outcomes than non-trial patients,[16] and lacked patient-level data for axi-cel.[17] A more recent real-world comparison, though limited by a small sample size of 87 patients and 11 months of follow-up, suggested similar outcomes between these products, with a propensity score matching analysis indicating superior progression-free survival (PFS) for axi-cel.[18]

To address the limitations of prior studies and provide a real-world, patient-level comparison of liso-cel and axi-cel, we utilized inverse probability of treatment weighting (IPTW). This statistical approach balances baseline characteristics between treatment groups to mitigate treatment allocation bias, enabling an unbiased assessment of the independent impact of CAR T-cell product type on outcomes in LBCL patients treated with liso-cel and axi-cel at our center per SOC.

Methods

Patients

The study was approved by Fred Hutchinson Cancer Center's (FHCC) Institutional Review Board based on federal regulations and the ethical standards of the FHCC Human Research Protection Program. Informed consent was obtained for the collection of medical data. All adult patients (age ≥18 years) with LBCL who received liso-cel or axi-cel at FHCC through May 2024 were included, with data collected through November 15, 2024.

Definitions

Definitions of LBCL subtypes, treatment response, adverse event grading, and other clinical criteria are detailed in the *Online Supplementary Appendix*.

Lymphodepletion chemotherapy

Patients received lymphodepletion chemotherapy with fludarabine and cyclophosphamide per product-specific FDA package inserts.[4,5]

Supportive care

Packed red blood cells and platelets were transfused for hematocrit <26% and platelet count <11×10^3/μL, respectively, or when clinically indicated. Broad-spectrum intravenous antibiotics were initiated for neutropenic fever per institutional guidelines. CRS and ICANS management followed product-specific risk evaluation and mitigation strategy and institutional guidelines.

Statistical analysis

All statistical analyses were conducted using R Statistical Software (Version 4.4.1; R Core Team 2024).[19] Continuous variables were compared with the Wilcoxon rank sum test, and categorical variables with Pearson's χ^2 test or Fisher's exact test. PFS was defined as time to death, relapse, or progressive disease (PD). Duration of response (DOR) was time to relapse, PD, or death for patients achieving CR or PR after CAR T-cell therapy. Overall survival (OS), PFS, and DOR were estimated using the Kaplan-Meier (KM) method. The cumulative incidence of relapse or progression was computed with tidycmprsk::cuminc() (Version 1.0.0), treating non-relapse mortality as a competing event. Median follow-up was determined using the reverse KM method. Binomial outcomes were assessed using univariate (UV) and multivariable (MV) logistic regression, and time-to-event outcomes with Cox regression. Logistic regression for CR was restricted to response-evaluable patients.

Inverse probability of treatment weighting

IPTW was employed to mitigate treatment allocation bias, while MV analysis addressed additional confounders. IPTW uses the inverse of the propensity score to create a weighted pseudo-population where covariates are balanced, enabling estimation of treatment effects as if treatments were randomly assigned. Unlike propensity score matching, IPTW retains all participants, preserving statistical power and providing an unbiased estimate of the average treatment effect.[20-22] Further details on the IPTW rationale and MV regression models are provided in the *Online Supplementary Appendix*.

Covariates for IPTW were selected based on subject-matter expertise regarding known and measurable confounders as described previously.[11,12,23,24] The following variables were included for IPTW: pre-leukapheresis lactate dehydrogenase (LDH; U/L; continuous), pre-leukapheresis absolute lymphocyte count (ALC; x10^3/μL; continuous), age (years; continuous), prior autologous hematopoietic cell transplantation (HCT; binary), use of CAR T-cell therapy in the second line setting (binary), Eastern Cooperative Oncology Group (ECOG) performance status ≥2 (binary), transformed LBCL *versus* other (binary), largest lesion diameter as measured on pre-infusion positron-emission tomography/computed tomography (PET/CT) (cm; continuous), presence of non-CNS extranodal disease (binary), presence of central nervous system (CNS) involvement (binary), HCT-specific comorbidity index (HCT-CI) score (continuous), and bridging response category (no bridging *vs*. complete reposnse/partial remission [CR/PR] after bridging *vs*. stable disease/disease progression [SD/PD] after bridging *vs*. bridging with unknown response).

Results

Patient characteristics prior to inverse probability of patient weighing

Between January 2018 and May 2024, 160 LBCL patients were treated with liso-cel (N=58) or axi-cel (N=102) at our center per SOC. Unweighted and IPTW patient characteristics are shown in Table 1. An out-of-specification product

was administered to 17 (11%) patients. Patients who received liso-cel were older (median age: 66 *vs*. 61 years; *P*=0.003) and experienced a longer median time interval from apheresis to CAR T-cell infusion (median time: 35 *vs*. 27 days; *P*<0.001; *Online Supplementary Figure S1*). There was numerically lower disease bulk in patients given liso-cel compared to axi-cel (median largest lesion: 3.1 *vs*. 3.5 cm; *P*=0.2). The distribution of bridging response categories differed for liso-cel *versus* axi-cel: no bridging, 41% *versus* 65%; CR/PR post-bridging, 26% *versus* 9.8%; and SD/PD post-bridging, 26% *versus* 25% (*P*<0.001). ECOG performance status and HCT-CI scores were similar between products. Prophylactic dexamethasone was used in one (1.7%) liso-cel and six (5.9%) axi-cel patients.

Inverse probability of patient weighing

For clarity, all summary statistics and estimates in the following sections refer to the pseudo-population generated by IPTW, unless otherwise specified.

The sample size of the pseudo-population after IPTW was 155 patients (liso-cel, N=55; axi-cel, N=100). IPTW resulted in good balance with an appropriate distribution of weights

Table 1. Inverse probability of treatment weighting and unweighted baseline characteristics of patients who received liso-cel and axi-cel.

Characteristic	IPTW			Unweighted		
	Liso-cel N=55	Axi-cel N=100	*P*[1]	Liso-cel N=58	Axi-cel N=102	*P*[2]
Age in years, median (IQR)	62 (52-69)	64 (53-68)	0.7	66 (56-73)	61 (50-67)	0.003
Male sex, N (%)	35 (63)	67 (67)	0.6	31 (53)	68 (67)	0.10
ECOG PS, N (%) 0-1 ≥2	 45 (82) 10 (18)	 82 (82) 18 (18)	 >0.9	 48 (83) 10 (17)	 81 (79) 21 (21)	 0.6
HCT-CI, median (IQR)	1.00 (0.00-3.00)	1.00 (1.00-3.00)	0.6	1.00 (0.00-3.00)	1.00 (1.00-3.00)	0.7
TRANSCEND eligible, N (%)	33 (59)	73 (73)	0.13	37 (64)	73 (72)	0.3
ZUMA-1 eligible, N (%)	32 (58)	53 (53)	0.6	35 (60)	57 (56)	0.6
Disease subtype, N (%) DLBCL HGBCL PMBCL TCHRLBCL tDLBCL	 33 (60) 5 (8.9) 0 (0) 3 (5.2) 14 (26)	 70 (70) 4 (4.0) 2 (2.1) 2 (1.8) 22 (22)	 0.3	 34 (59) 8 (14) 0 (0) 2 (3.4) 14 (24)	 74 (73) 5 (4.9) 3 (2.9) 2 (2.0) 18 (18)	 0.11
Largest lesion in cm, median (IQR)	3.5 (0.0-4.8)	3.5 (2.2-6.2)	0.3	3.1 (0.9-4.8)	3.5 (2.0-6.5)	0.2
Extranodal, N (%)	31 (56)	61 (61)	0.6	32 (55)	62 (61)	0.5
CNS, N (%)	2 (4.0)	3 (3.3)	0.8	4 (6.9)	3 (2.9)	0.3
LDH pre-LD U/L, median (IQR) Unknown	179 (151-246)	198 (148-310)	0.3	177 (146-246) 0	210 (155-313) 1	0.12
LDH, pre-leuka U/L, median (IQR)	188 (158-272)	218 (168-317)	0.13	190 (158-272)	220 (168-364)	0.11
ALC, pre-LD x10^3/μL, median (IQR)	0.55 (0.38-0.82)	0.54 (0.30-1.03)	>0.9	0.64 (0.38-0.96)	0.58 (0.31-0.99)	0.4
ALC pre-leuka x10^3/μL, median (IQR)	0.56 (0.46-0.79)	0.57 (0.38-0.90)	0.5	0.64 (0.48-0.99)	0.59 (0.37-0.92)	0.3
Plt, pre-leuka x10^3/μL, median (IQR)	146 (107-185)	138 (96-196)	0.7	141 (99-185)	139 (99-208)	0.8
Second line, N (%)	5 (9.4)	10 (9.9)	>0.9	8 (14)	7 (6.9)	0.15
Prior ASCT, N (%)	9 (17)	18 (18)	>0.9	6 (10)	21 (21)	0.10
Bridging response category, N (%) No bridging CR/PR SD/PD Unknown response	 31 (57) 10 (18) 12 (23) 1 (2.6)	 57 (57) 17 (17) 26 (26) 0 (0)	 0.4	 24 (41) 15 (26) 15 (26) 4 (6.9)	 66 (65) 10 (9.8) 26 (25) 0 (0)	 <0.001
Out-of-specification, N (%)	14 (26)	1 (1.5)	<0.001	15 (26)	2 (2.0)	<0.001

[1]Design-based KruskalWallis test; Pearson's χ^2: Rao and Scott adjustment. [2]Wilcoxon rank sum test; Pearson's χ^2 test; Fisher's exact test. IPTW: inverse probability of treatment weighting; ECOG: Eastern cooperative oncology group; PS: performance status; HCT-CI: hematopoietic cell transplantation-comorbidity index; ASCT: autologous stem cell transplant; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; DLBCL: diffuse large B-cell lymphoma; HGBCL: high grade B-cell lymphoma; PMBCL: primary mediastinal B-cell lymphoma; TCHRLBCL: T-cell/histiocyte-rich large B-cell lymphoma; tDLBCL: transformed DLBCL; CNS: central nervous system; LDH: lactate dehydrogenase; Plt: platelet; ALC: absolute lymphocyte count; leuka: leukapheresis; LD: lymphodepleting; IQR: interquartile range; axi-cel: axicabtagene ciloleucel; liso-cel: lisocabtagene maraleucel.

(*Online Supplemental Figure S2*). After matching the covariates, all absolute standardized mean differences were <0.2 indicating adequate balance.[25] The variance ratios of the continuous variables were 1.46 for age, 0.50 for largest lesion diameter, 9.1 for pre-leukapheresis LDH, 0.18 for pre-leukapheresis ALC, and 1.4 for HCT-CI.

Patient characteristics following IPTW are shown in Table 1, where patient numbers are rounded to the nearest integer. The median age was 63 years (IQR, 53-68) and 66% (N=102) were male. A minority received CAR T-cell therapy as second line (9.7%, N=15) or had undergone prior autologous HCT (17%, N=27). A significant proportion of patients did not meet the eligibility criteria for the TRANSCEND-NHL-001 (32%, N=50) or ZUMA-1 (46%, N=71) clinical trials. Most patients had DLBCL (67%, N=103) or transformed DLBCL (23%, N=36). Other disease categories included high-grade B-cell lymphoma (5.7%, N=9), primary mediastinal large B-cell lymphoma (1.3%, N=2), and T-cell/histiocyte-rich LBCL (3.0%, N=5).

Toxicity

All patients were evaluable for toxicity assessment. IPTW and unweighted rates of CRS, ICANS, and ICAHT are depicted in Figure 1. For liso-cel *versus* axi-cel, unadjusted IPTW toxicities were as follows: any-grade CRS, 68% *versus* 88% (*P*=0.011); grade 2+ CRS, 25 *versus* 50% (*P*=0.008); grade 3+ CRS, 3.1% *versus* 7.5% (*P*=0.4); any-grade ICANS, 35% *versus* 55% (*P*=0.041); grade 2+ ICANS, 28% *versus* 42% (*P*=0.12); grade 3+ ICANS, 19% *versus* 20% (*P*>0.9); any-grade ICAHT, 63% *versus* 92% (*P*<0.001); grade 2+ ICAHT, 19% *versus* 49% (*P*=0.001); and grade 3+ ICAHT, 7.3% *versus* 19% (*P*=0.049). Fewer liso-cel patients received tocilizumab (32% *vs*. 55%; *P*=0.017) and non-prophylactic dexamethasone (38% *vs*. 64%; *P*=0.007). The proportion of liso-cel and axi-cel patients who received granulocyte colony-stimulating factor (G-CSF) was similar (72% *vs*. 81%; *P*=0.3), though liso-cel patients received fewer median doses (2 *vs*. 5; *P*=0.006). None received peg-G-CSF. IPTW and unweighted peak inflammatory markers are shown in *Online Supplementary Table S1*. We measured lower median peak serum CRP (71 *vs*. 114 mg/dL; *P*=0.002), D-dimer (1.3 *vs*. 2.4 mg/L; *P*=0.011), ferritin (666 *vs*. 1,081 ng/mL; *P*=0.009), IL-6 (55 *vs*. 196 ng/mL; *P*=0.030), and ALT (32 *vs*. 51 U/L; *P*=0.020) after liso-cel treatment compared to axi-cel.

Post-infusion median nadir cytopenias were less severe after liso-cel: ANC, 0.34 *versus* 0.04x10³/μL (*P*<0.001); hemoglobin, 8.80 *versus* 8.20 g/dL (*P*=0.015); and platelets, 84 *versus* 35x10³/μL (*P*=0.002). Fewer patients developed severe neutropenia after liso-cel, 63% *vs*. 92% (*P*<0.001), and the median duration of neutropenia was shorter, 2.0 *versus* 6.0 days (*P*<0.001). Unweighted longitudinal ANC and platelet count data are shown in *Online Supplementary Figure S3*. At day +30, the median platelet count was higher for liso-cel compared to axi-cel (101 *vs*. 63x10³/μL; *P*=0.045), but otherwise median laboratory values were comparable: ANC, 1.56 *versus* 1.37x10³/μL (*P*=0.2); and hemoglobin, 10.60 *versus* 10.20 g/dL (*P*=0.11).

The incidence of infectious complications (*Online Supplementary Table S2*) after liso-cel *versus* axi-cel was as follows: bacteremia, 3.6% *versus* 8.3% (*P*=0.3); Cytomegalovirus (CMV) viremia, 32% *versus* 28% (*P*=0.6); and CMV level ≥150 IU/mL (threshold requiring anti-viral therapy per our standard practice), 7.5% *versus* 5.8% (*P*=0.7). Fewer liso-cel patients received cefepime (43% *vs*. 71%; *P*=0.003).

While axi-cel patients were required to remain inpatient for at least 7 days following infusion, liso-cel had no mandatory inpatient stay and was administered in an outpatient setting for 39% of patients (N=21). Compared to axi-cel, liso-cel patients experienced significantly shorter total inpatient duration (5 *vs*. 14 days; *P*<0.001), and a smaller proportion required 2+ admissions (5.1% *vs*. 25%; *P*<0.001). Both metrics were assessed from the day of infusion through day +30. Of note, 14 patients (liso-cel: 11; axi-cel: 3) were in CR at the time of lymphodepletion chemotherapy, and none experienced grade 3+ CRS, ICANS, or early ICAHT. The incidence of any-grade toxicity was as follows for liso-cel compared to axi-cel: CRS, 50% *versus* 46%; ICANS 12% *versus* 24%; and early ICAHT, 39% *versus* 46%.

Response rates

IPTW and unweighted responses to CAR T-cell therapy in response-evaluable patients are shown in Table 2. Among response-evaluable patients (N=141), we observed comparable best response rates with liso-cel *versus* axi-cel: ORR, 76% *versus* 78% (*P*=0.8); and CR, 46% *versus* 49% (*P*=0.8). The proportions of patients who converted from an initial PR to a CR were similar across CAR T-cell products (liso-cel *vs*. axi-cel: 11% *vs*. 7.0%; *P*=0.4). Among responders, the median time to best response was similar (liso-cel *vs*. axi-cel: 28 *vs*. 29 days; *P*=0.12).

Among patients who received bridging therapy and were evaluable for response (N=62), the best response rates were comparable for liso-cel *versus* axi-cel: ORR, 73% *versus* 74% (*P*>0.9); and CR, 34% *versus* 40% (*P*=0.7).

Long-term outcomes

Kaplan-Meier plots depicting OS, PFS and DOR, and cumulative incidence plots depicting relapse and non-relapse mortality (NRM), are shown in Figure 2. The median follow-up was 35.3 months (liso-cel, 29.8; axi-cel, 53.8). The median OS, PFS, and DOR were 41.1 months (95% CI: 13.6-not reached), 10.7 months (95% CI: 5.7-29.3), and 28.4 months (95% CI: 15.4-not reached), respectively. Median OS (liso-cel, not reached; axi-cel, 16.3 months; *P*=0.12), PFS (liso-cel, 11.9; axi-cel, 10.7 months; *P*=0.89), DOR (liso-cel, 21.4 *vs*. 38.4 months; *P*=0.78), and 3-year cumulative incidence of relapse (53.2% *vs*. 46.2%; *P*=0.69) were not significantly different between products. Unweighted survival plots are shown in *Online Supplementary Figure S4*.

We next evaluated outcomes in high-risk patients spe-

cifically. For liso-cel *versus* axi-cel, the OS and PFS were assessed among patients with bulky disease (largest lesion diameter ≥5 cm; OS: 6.8 *vs*. 7.2 months; *P*=0.91; PFS: 4.7 *vs*. 3.0 months; *P*=0.91), high LDH (≥210 U/L; OS: 13.6 *vs*. 12.1 months; *P*=0.62; PFS: 7.2 *vs*. 5.7 months; *P*=0.84), extranodal disease (OS: not reached *vs*. 16.3 months; *P*=0.4; PFS: 6.8

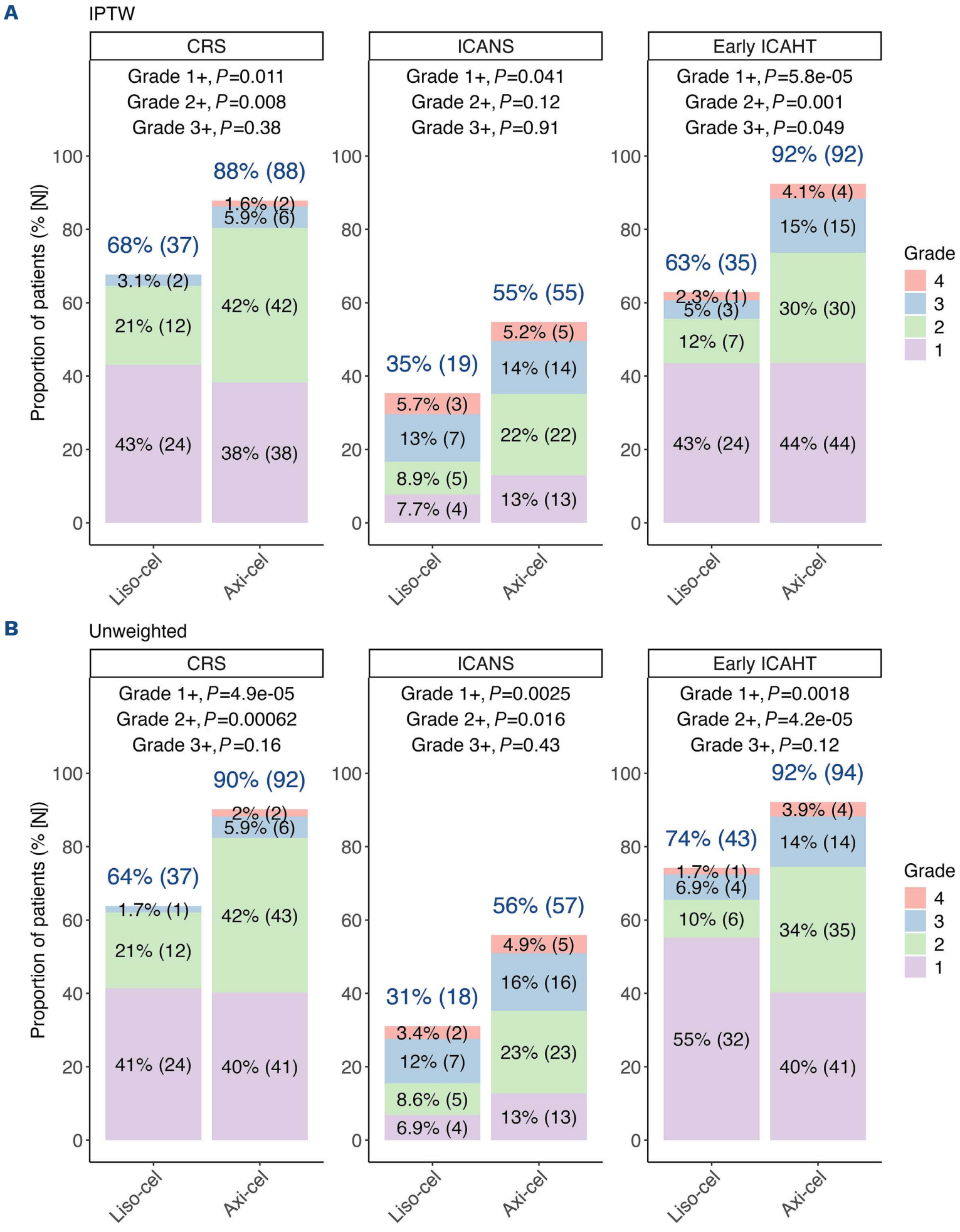

Figure 1. Comparative analysis of toxicities between CAR T-cell product types. (A) Inverse probability of treatment weighting (IPTW) and (B) unweighted comparisons of cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and early immune effector cell-associated hematotoxicity (ICAHT). Weighted patient numbers have been rounded to the nearest integer. *P* values for comparisons of toxicities were derived from the χ^2 test or Fisher's exact test (with Rao and Scott's second-order correction for IPTW comparisons). CAR: chimeric antigen receptor; axi-cel: axicabtagene ciloleucel; liso-cel: lisocabtagene maraleucel.

vs. 5.7; *P*=0.83), or who received bridging therapy (OS: 12.0 *vs*. 9.5 months; *P*=0.83; PFS: 4.0 *vs*. 5.7; *P*=0.22), as depicted in Figures 3 and 4, respectively.

Trial-eligible patients demonstrated superior OS (ZUMA-1: not reached *vs*. 12.0 months; *P*=0.003; TRANSCEND: 51.1 *vs*. 16.0 months; *P*=0.051) and PFS (ZUMA-1: 22.6 *vs*. 5.1 months; *P*=0.019; TRANSCEND: 15.9 *vs*. 5.3 months; *P*=0.15), as shown in *Online Supplementary Figures S5* and *S6*, respectively. Unweighted comparisons are shown in *Online Supplementary Figures S7* and *S8,* respectively.

Among patients not in a CR at time of lymphodepletion chemotherapy (liso-cel: 44 patients; axi-cel: 97 patients), the median duration of follow-up was 38.0 months (liso-cel: 26.5 months; axi-cel 53.8 months). No significant differences were observed between liso-cel and axi-cel in terms of median OS (not reached *vs*. 24.3 months; *P*=0.57), PFS (5.1 *vs*. 10.7 months; *P*=0.38), or DOR (11 *vs*. 38.4 months; *P*=0.32). Additionally, the 1-year cumulative incidence of relapse was comparable between liso-cel and axi-cel (52.8% *vs*. 43.3%; *P*=0.28), as shown in *Online Supplementary Figure S9*.

Among the 14 patients in a CR at the time of lymphodepletion chemotherapy (liso-cel: 11; axi-cel: 3), one axi-cel patient experienced an early relapse at 27 days. Excluding this case, the 1-year PFS was 88% for liso-cel and 100% for axi-cel, while 1-year OS was excellent for both groups at 100%.

Regression models estimating the effect of the CAR T-cell product type on outcomes

Efficacy

In IPTW UV and MV analyses (Table 3), we did not observe an independent impact of the product type (reference: liso-cel) on CR (adjusted OR [aOR] for axi-cel: 1.12, 95% CI: 0.52-2.40; *P*=0.8), DOR (aHR for axi-cel: 0.89, 95% CI: 0.48-1.65; *P*=0.7), relapse (aHR for axi-cel: 0.92, 95% CI: 0.55-1.54; *P*=0.8), PFS (aHR for axi-cel: 0.97, 95% CI: 0.60-1.56; *P*=0.9), or OS (aHR for axi-cel: 1.34, 95% CI 0.73-2.47; *P*=0.3). Similar findings were noted in unweighted analyses (*Online Supplementary Table S3*).

In IPTW MV analysis, increasing pre-leukapheresis LDH remained independently associated with lower odds of a CR, and increased hazard of PFS and OS.

Among patients not in a CR at time of lymphodepletion chemotherapy, we did not observe an independent impact of product type (reference: liso-cel) on PFS (aOR for axi-cel: 0.80, 95% CI: 0.47-1.36; *P*=0.4), DOR (aOR for axi-cel: 0.76, 95% CI: 0.40-1.46; *P*=0.4), or OS (aOR for axi-cel: 1.13, 95% CI: 0.61-2.10; *P*=0.7).

Toxicity

In all models, axi-cel (reference: liso-cel) was associated with higher odds of any-grade CRS, ICANS, and early ICAHT; and grade 2+ CRS and early ICAHT. In IPTW MV analysis, the aOR for axi-cel for any-grade CRS was 4.27 (95% CI: 1.59-11.4; *P*=0.004), for grade 2+ CRS was 2.88 (95% CI: 1.36-6.14; *P*=0.006), for any-grade ICANS was 2.10 (95% CI: 1.01-4.40; *P*=0.048), for any-grade early ICAHT was 8.09 (95% CI: 2.87-22.8; *P*<0.001), and for grade 2+ early ICAHT was 3.86 (95% CI: 1.72-8.65; *P*=0.001). In IPTW MV analysis, we did not detect significantly higher odds of grade 3+ toxicities (CRS: aOR=1.50, 95% CI: 0.24-9.30; *P*=0.7; ICANS: aOR=0.97, 95% CI: 0.39-2.38; *P*>=0.9; early ICAHT: aOR=3.46, 95% CI: 0.96-12.5; *P*=0.057).

In IPTW MV analysis, increasing largest lesion size re-

Table 2. Inverse probability of treatment weighting and unweighted response assessments among response-evaluable patients.

Characteristic	IPTW			Unweighted		
	Liso-cel N=44	Axi-cel N=97	*P*[1]	Liso-cel N=48	Axi-cel N=99	*P*[2]
Initial response, N (%) CR PR SD PD	 15 (35) 17 (39) 1 (1.4) 10 (24)	 41 (42) 34 (35) 2 (1.7) 20 (21)	0.9	 13 (27) 21 (44) 1 (2.1) 13 (27)	 41 (41) 35 (35) 2 (2.0) 21 (21)	0.4
Best response, N (%) CR PR SD PD	 20 (46) 13 (30) 0 (0) 10 (24)	 48 (49) 28 (29) 1 (1.0) 20 (21)	>0.9	 20 (42) 15 (31) 0 (0) 13 (27)	 47 (47) 30 (30) 1 (1.0) 21 (21)	0.8
CR, N (%)	20 (46)	48 (49)	0.8			
PD, N (%)	10 (24)	20 (21)	0.7	13 (27)	21 (21)	0.4
ORR, N (%)	33 (76)	75 (78)	0.8	35 (73)	77 (78)	0.5
Conversion to CR, N (%)	5 (11)	7 (7.0)	0.4	7 (15)	6 (6.1)	0.12

[1]Pearson's χ^2: Rao and Scott adjustment. [2]Fisher's exact test; Pearson's χ^2 test. IPTW: inverse probability of treatment weighting; CR: complete response; PD: progressive disease; PR: partial response; SD: stable disease; ORR: overall response rate; axi-cel: axicabtagene ciloleucel; liso-cel: lisocabtagene maraleucel.

mained associated with higher odds of any-grade CRS and any-grade/grade 2+/grade 3+ ICANS; and increasing pre-leukapheresis LDH was associated with higher odds any-grade/grade 3+ CRS, any-grade ICANS, and grade 2+ ICAHT.

Additionally, in IPTW MV analysis, axi-cel (reference: liso-cel) was associated with higher odds of receiving tocilizumab (aOR=2.50, 95% CI: 1.17-5.34; *P*=0.017), dexamethasone (aOR=2.77, 95% CI: 1.31-5.83; *P*=0.007), and cefepime (aOR=3.37, 95% CI: 1.62-7.01; *P*=0.001).

Sensitivity analyses

Sensitivity analysis #1: contemporaneous cohort

To evaluate the impact of CAR T-cell product type on outcomes in a contemporaneous cohort, we analyzed patients treated between April 2021 and May 2024, after the introduction of liso-cel at our institution. During this period, 58 patients received liso-cel and 34 received axi-cel. Absolute standardized mean differences are shown in *Online Supplementary Figure S10*.

IPTW MV regression analysis (Figure 5) could not confirm

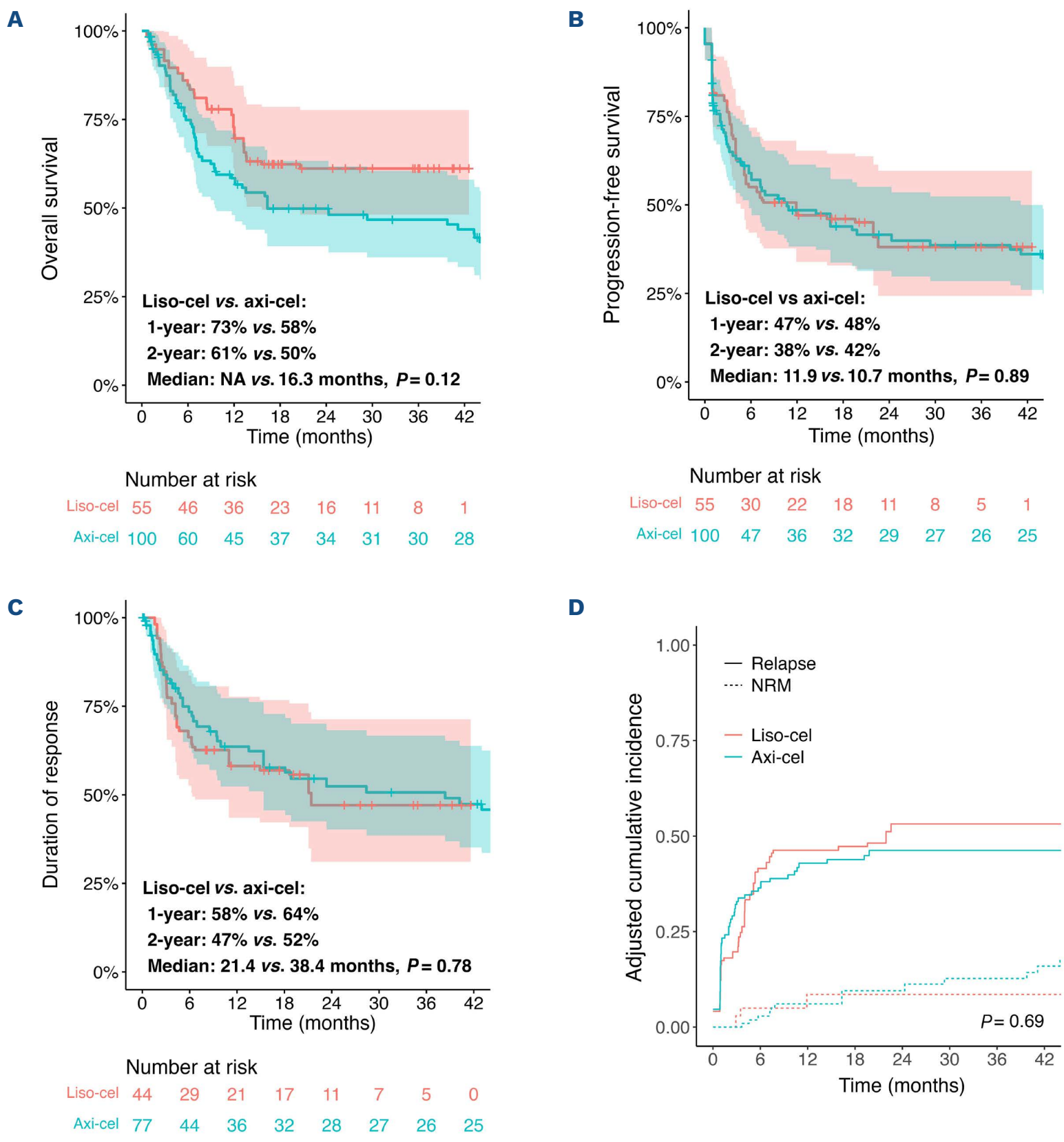

Figure 2. Analysis of survival outcomes and non-relapse mortality. Inverse probability of treatment weighting Kaplan-Meier plots, stratified by product type, showing (A) overall survival, (B) progression-free survival, (C) duration of response, and (D) cumulative incidence of relapse, and non-relapse mortality (NRM). Median survival times were analyzed using weighted univariate Cox regression, and the 1-year cumulative incidence of relapse was assessed with Gray's test. axi-cel: axicabtagene ciloleucel; liso-cel: lisocabtagene maraleucel; NA: not applicable.

differences in efficacy outcomes between liso-cel and axi-cel (reference: liso-cel) for CR (aOR=1.01, 95% CI: 0.39-2.58; *P*>0.9), DOR (aHR=1.0, 95% CI: 0.50-2.02; *P*>0.9), PFS (aHR=1.02, 95% CI: 0.57-1.83; *P*>0.9), or OS (aHR=1.31, 95% CI: 0.60-2.82; *P*=0.5). However, axi-cel was associated with higher odds of grade 1+ CRS (aOR=18, 95% CI: 2.57-126; *P*=0.022) and grade 2+ CRS (aOR=2.98, 95% CI: 1.17-7.58; *P*=0.022). In UV analysis, axi-cel was associated with grade 1+ ICANS (OR=2.47, 95% CI: 1.03-5.93; *P*=0.042), although this did not reach statistical significance in MV analysis (aOR=2.53, 95% CI: 0.90-7.12; *P*=0.078).

No significant differences were observed between product types for early ICAHT outcomes. Notably, axi-cel patients treated during this period had significantly higher G-CSF use compared to their earlier counterparts (98% *vs*. 72%; *P*<0.001; median 8 *vs*. 3 doses; *P*<0.001) and compared to liso-cel patients (98% *vs*. 72%; *P*<0.001; median 8 *vs*. 2 doses; *P*<0.001). These differences, shown in *Online Supplementary Figure S11*, may have contributed to ICAHT outcomes.

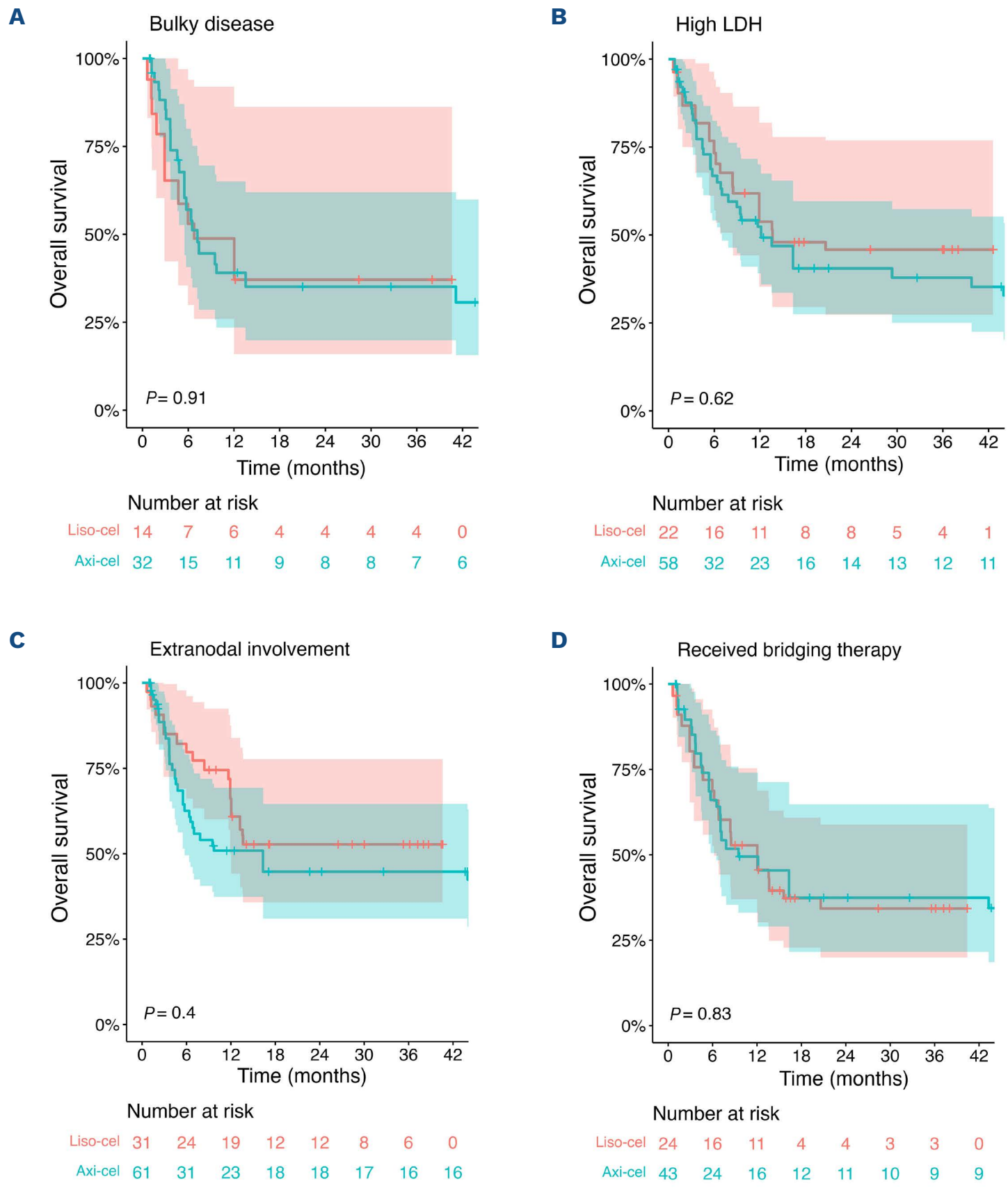

Figure 3. Kaplan-Meier analysis of overall survival in patient subgroups. Inverse probability of treatment weighting Kaplan-Meier plots depicting overall survival of patients with (A) bulky disease (largest lesion diameter ≥5 cm), (B) high lactate dehydrogenase (LDH) (≥210 U/L), (C) extranodal involvement, and (D) who received bridging therapy. *P* values were derived from weighted univariate Cox regressio to axi-cel: axicabtagene ciloleucel; liso-cel: lisocabtagene maraleucel.

Table 3. Summary of inverse probability of treatment weighting univariate and multivariable regression analyses.

	Univariate			Multivariable		
CR	**OR**	**95% CI**	***P***	**aOR**	**95% CI**	***P***
Product Liso-cel Axi-cel	- 1.12	- 0.55-2.28	0.8	- 1.12	- 0.52-2.40	0.8
Pre-leuka LDH	0.14	0.03-0.65	0.012	0.16	0.03-0.88	0.035
Pre-leuka ALC	1.49	0.75-2.95	0.3	1.54	0.73-3.24	0.3
Largest lesion	0.93	0.84-1.03	0.15	0.99	0.88-1.11	0.9
DOR	**HR**	**95% CI**	***P***	**aHR**	**95% CI**	***P***
Product Liso-cel Axi-cel	- 0.92	- 0.49-1.70	0.8	- 0.89	- 0.48-1.65	0.7
Pre-leuka LDH	7.02	2.34-21.1	<0.001	3.37	0.62-18.4	0.2
Pre-leuka ALC	0.74	0.36-1.52	0.4	0.78	0.43-1.43	0.4
Largest lesion	1.07	0.99-1.17	0.1	0.97	0.84-1.10	0.6
Relapse	**HR**	**95% CI**	***P***	**aHR**	**95% CI**	***P***
Product Liso-cel Axi-cel	- 0.97	- 0.58-1.65	>0.9	- 0.92	- 0.55-1.54	0.8
Pre-leuka LDH	2.63	1.38-5.00	0.003	1.54	0.63-3.74	0.3
Pre-leuka ALC	0.88	0.52-1.50	0.6	0.93	0.66-1.32	0.7
Largest lesion	1.06	0.98-1.14	0.15	1	0.92-1.08	>0.9
PFS	**HR**	**95% CI**	***P***	**aHR**	**95% CI**	***P***
Product Liso-cel Axi-cel	- 1.04	- 0.63-1.70	0.9	- 0.97	- 0.60-1.56	0.9
Pre-leuka LDH	3.61	2.10-6.21	<0.001	2.15	1.09-4.23	0.027
Pre-leuka ALC	0.8	0.41-1.58	0.5	0.89	0.59-1.36	0.6
Largest lesion	1.08	1.02-1.15	0.012	1.02	0.95-1.10	0.6
OS	**HR**	**95% CI**	***P***	**aHR**	**95% CI**	***P***
Product Liso-cel Axi-cel	- 1.56	- 0.89-2.74	0.12	- 1.34	- 0.73-2.47	0.3
Pre-leuka LDH	9.11	4.26-19.5	<0.001	4.78	1.53-15.0	0.007
Pre-leuka ALC	0.87	0.44-1.71	0.7	0.97	0.67-1.40	0.9
Largest lesion	1.13	1.06-1.21	<0.001	1.06	0.98-1.16	0.2
CRS, any grade	**OR**	**95% CI**	***P***	**aOR**	**95% CI**	***P***
Product Liso-cel Axi-cel	- 3.46	- 1.52-7.89	0.003	- 4.27	- 1.59-11.4	0.004
Pre-leuka LDH	145	7.41-2,835	0.001	104	3.16-3,411	0.009
Pre-leuka ALC	1.99	0.70-5.64	0.2	2.41	0.64-9.04	0.2
Largest lesion	1.29	1.08-1.54	0.004	1.29	1.07-1.56	0.007
CRS, grade 2+	**OR**	**95% CI**	***P***	**aOR**	**95% CI**	***P***
Product Liso-cel Axi-cel	- 3.03	- 1.46-6.27	0.003	- 2.88	- 1.36-6.14	0.006
Pre-leuka LDH	4.72	1.17-19.0	0.029	4.34	0.93-20.3	0.062
Pre-leuka ALC	1.05	0.72-1.53	0.8	1.06	0.71-1.57	0.8
Largest lesion	1.07	0.97-1.17	0.2	1.07	0.96-1.20	0.2
ICANS, any grade	**OR**	**95% CI**	***P***	**aOR**	**95% CI**	**P**
Product Liso-cel Axi-cel	- 2.21	- 1.12, 4.37	0.022	- 2.1	- 1.01-4.40	0.048
Pre-leuka LDH	14.1	2.81, 70.9	0.001	6.5	1.22-34.7	0.029
Pre-leuka ALC	1.05	0.71-1.55	0.8	1.11	0.74-1.66	0.6
Largest lesion	1.2	1.08-1.34	<0.001	1.17	1.04-1.31	0.01

Continued on following page.

	Univariate			Multivariable		
Early ICAHT, any grade	**OR**	**95% CI**	***P***	**aOR**	**95% CI**	***P***
Product Liso-cel Axi-cel	- 7.22	- 2.87-18.2	<0.001	- 8.09	- 2.87-22.8	<0.001
Pre-leuka LDH	80.4	4.45-1,451	0.003	19.7	0.57-685	0.1
Pre-leuka ALC	1.32	0.54-3.25	0.5	1.32	0.35-5.04	0.7
Largest lesion	1.27	1.07-1.52	0.008	1.08	0.87-1.33	0.5
Early ICAHT, grade 2+	**OR**	**95% CI**	***P***	**aOR**	**95% CI**	***P***
Product Liso-cel Axi-cel	- 3.97	- 1.83-8.61	<0.001	- 3.86	- 1.72-8.65	0.001
Pre-leuka LDH	6.79	1.60-28.8	0.009	6.02	1.10-33.0	0.039
Pre-leuka ALC	1.01	0.69-1.48	>0.9	1	0.59-1.71	>0.9
Largest lesion	1.04	0.95-1.14	0.4	1.01	0.90-1.13	0.9

axi-cel: axicabtagene ciloleucel; liso-cel: lisocabtagene maraleucel; CR: complete response; DOR: duration of response; PFS: progression-free survival; OS: overall survival; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome; ICAHT: immune effector cell-associated hematotoxicity; OR: odds ratio; aOR: adjusted OR; HR: hazard ratio; aHR: adjusted HR; CI: confidence interval; LDH: lactate dehydrogenase; ALC: absolute lymphocyte count; LD: lymphodepleting; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease. The predictors were scaled as follows: LDH was log10-transformed (U/L), ALC was scaled to x10^3 cells/μL, and the size of the largest lesion was measured in 1 cm units.

Sensitivity analysis #2: baseline inflammatory markers

To evaluate the influence of baseline inflammatory markers, IPTW was performed using day 0 ferritin and CRP (available for 147 and 146 patients, respectively). Absolute standardized mean differences are shown in *Online Supplementary Figure S10*.

As summarized in Figure 5, no significant differences were found between liso-cel and axi-cel (reference: liso-cel) for CR (aOR=1.51, 95% CI: 0.65-3.47), DOR (aHR=1.02, 95% CI: 0.52-2.02; *P*>0.9), PFS (aHR=1.06, 95% CI 0.62-1.80; *P*=0.8), or OS (aHR 1.72, 95% CI: 0.84-3.51; *P*=0.14). Axi-cel was associated with higher odds of grade 1+ CRS (aOR=4.41, 95% CI: 1.39-13.9; *P*=0.012), grade 2+ CRS (aOR=3.15, 95% CI: 1.40-7.07; *P*=0.005), any-grade ICANS (aOR=2.75, 95% CI: 1.19-6.34; *P*=0.018), grade 1 eICAHT (aOR=7.05, 95% CI: 2.28-21.8; *P*<0.001), and grade 2 eICAHT (aOR=4.27, 95% CI: 1.74-10.5; *P*=0.002).

Sensitivity analysis #3: disease activity (maximum standardized uptake value)

To examine the role of disease activity, we performed IPTW incorporating the maximum tandardized uptake value (SUV) from pre-CAR-T PET/CT scans from 153 available patients. Absolute standardized mean differences are shown in *Online Supplementary Figure S10*.

As shown in Figure 5, showed no significant differences were observed between liso-cel and axi-cel (reference: liso-cel) for CR (aOR=1.66, 95% CI: 0.78-3.63; *P*=0.2), DOR (aHR=0.84, 95% CI: 0.46-1.55; *P*=0.6), PFS (aHR=0.83, 95% CI: 0.51-1.35; *P*=0.5), or OS (aHR=1.32, 95% CI: 0.72-2.43; *P*=0.4). Axi-cel was associated with higher odds of grade 1+ CRS (aOR=7.08, 95% CI: 2.24-22.4; *P*<0.001), grade 2+ CRS (aOR=3.33, 95% CI: 1.51-7.34; *P*=0.003), grade 1 eICAHT (aOR=6.15, 95% CI: 2.06-18.4; *P*=0.001), and grade 2 eICAHT (aOR=2.72, 95% CI: 1.23-6.01; *P*=0.013). No significant association between axi-cel and any-grade ICANS was observed in UV (OR=1.64, 95% CI: 0.85-3.14; *P*=0.14) or MV (aOR=1.78, 95% CI: 0.84-3.75; *P*=0.13) models, though the effect sizes were similar to the other models.

Discussion

CD19 CAR T-cell therapies have revolutionized the management of patients with high risk or R/R LBCL, though their use remains limited by significant toxicities. Retrospective analyses suggest axi-cel may offer stronger anti-tumor activity than tisa-cel, albeit with increased toxicity.[11,12] Liso-cel, more recently approved by the FDA and EMA for high-risk or R/R LBCL, has demonstrated high efficacy with lower rates of severe CRS and ICANS in single-arm studies, making it an appealing option for older or frail patients.[13,14,26] However, real-world data comparing these therapies are limited. A prior study of 87 patients (50 treated with axi-cel and 27 with liso-cel) with 11 months of follow-up suggested superior PFS with axi-cel but did not adjust for key confounders such as response to bridging therapy or the presence of extranodal disease, particularly CNS involvement.[18,23,24] Using a larger cohort of 160 patients and nearly 3 years of follow-up, our analysis employed IPTW to account for all known factors impacting treatment allocation and survival outcomes, enabling a more robust real-world comparison of the two CAR T-cell products.

Baseline differences in patient characteristics reflected treatment allocation bias. Liso-cel patients were older (66 *vs.* 61 years) and more likely to receive CAR T-cell treatment as second-line therapy, while axi-cel patients had greater tumor burden and were less likely to respond to

bridging therapy. These trends likely reflect a preference for liso-cel in older or frail patients, axi-cel being approved for a longer duration in the third-line setting, and a tendency to reserve axi-cel for patients with greater disease burden. To mitigate these biases, IPTW was applied to balance key confounders influencing treatment allocation.

We estimated comparable anti-tumor efficacy between the two CAR T-cell products. The ORR were nearly identical (liso-cel *vs*. axi-cel: 76% *vs*. 78%) among response-evaluable patients, while CR rates were similar (liso-cel *vs*. axi-cel: 46% *vs*. 49%). These CR rates were lower than those reported in clinical trials for liso-cel (TRANSCEND-NHL-001: 53%; TRANSFORM: 66%) and axi-cel (ZUMA-1: 54%; ZUMA-7: 65%).[2,3,14,27] Median OS and PFS showed no significant differences for liso-cel *versus* axi-cel, with OS favoring liso-cel (not reached *vs*. 16.3 months) and PFS showing minimal variation (11.9 *vs*. 10.7 months). Although liso-cel demonstrated a numerically shorter DOR compared to axi-cel (21.4

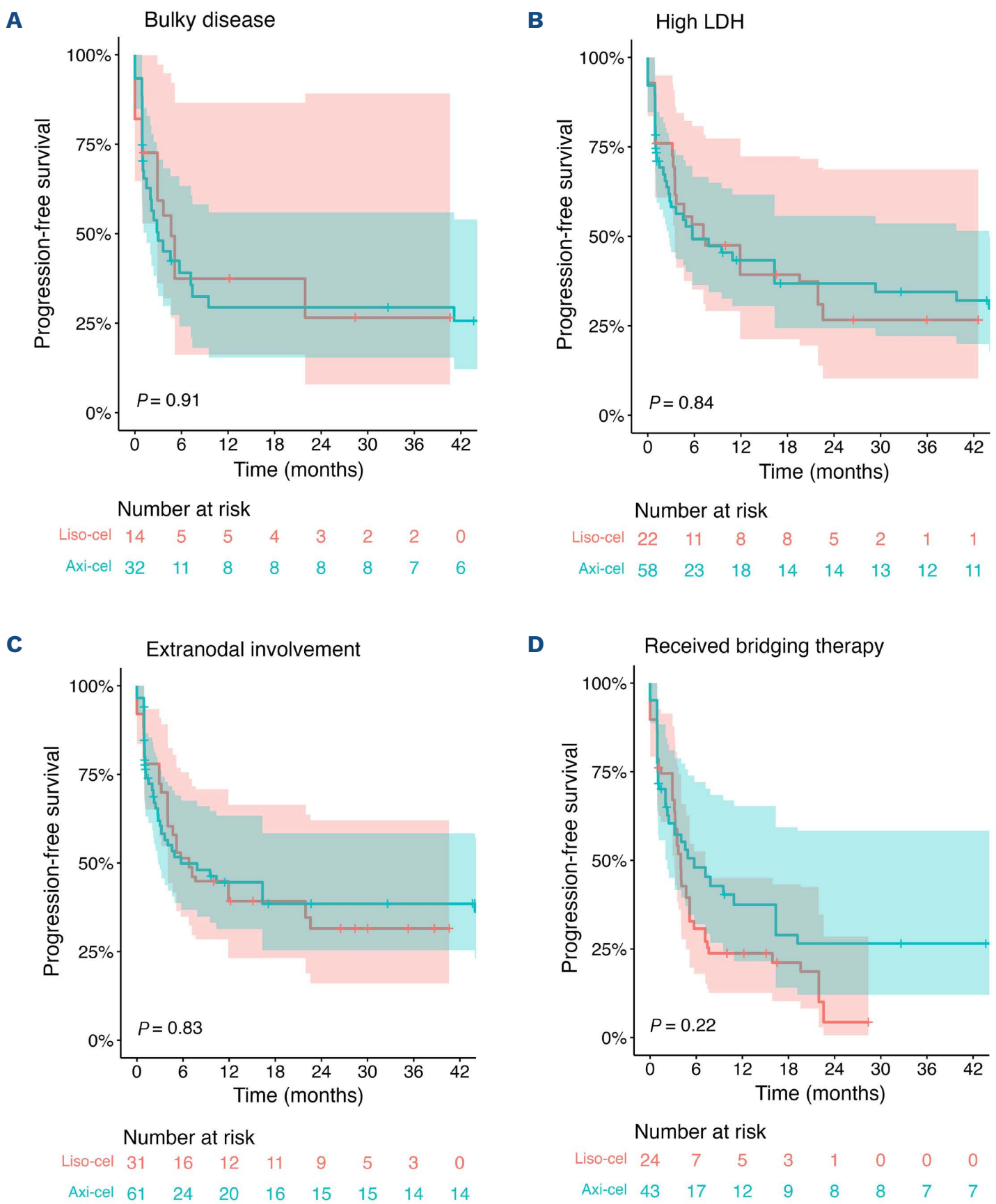

Figure 4. Kaplan-Meier analysis of progression-free survival in patient subgroups. Inverse probability of treatment weighting Kaplan-Meier plots depicting progression-free survival of patients with (A) bulky disease (largest lesion diameter ≥5 cm), (B) high lactate dehydrogenase (LDH) (≥210 U/L), (C) extranodal involvement, and (D) who received bridging therapy. *P* values were derived from weighted univariate Cox regression. axi-cel: axicabtagene ciloleucel; liso-cel: lisocabtagene maraleucel.

vs. 38.4 months) - particularly among patients not in CR at the time of lymphodepletion (PFS: 5.1 *vs*. 10.7 months; DOR: 11 *vs*. 38.4 months) - these differences did not reach statistical significance. These findings suggest that both liso-cel and axi-cel are excellent options for high-risk and/or R/R LBCL patients. Notably, our IPTW-adjusted estimates

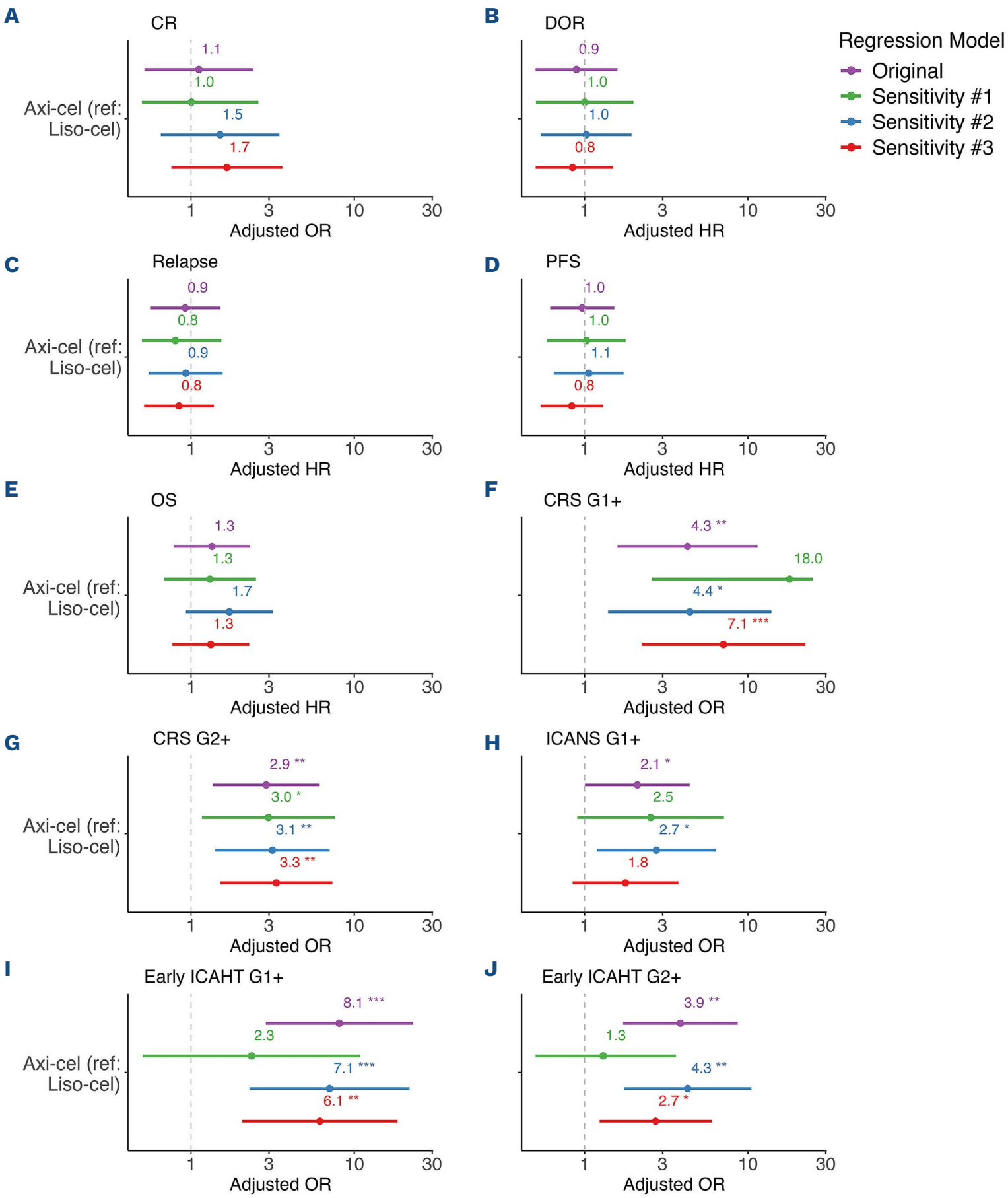

Figure 5. Sensitivity analyses of response, survival, and toxicity outcomes. Sensitivity analyses evaluating: (A) complete response (CR), (B) duration of response (DOR), (C) relapse rate, (D) progression-free survival (PFS), (E) overall survival (OS), (F) cytokine release syndrome (CRS) grade 1 (G1) or higher, (G) CRS grade 2 or higher, (H) immune effector cell-associated neurotoxicity syndrome (ICANS) G1 or higher, (I) early immune effector cell-associated hematotoxicity (ICAHT) G1 or higher, and (J) early ICAHT G2 or higher. Three inverse probability of treatment weighting models were compared: the original model, Sensitivity #1 (restricted to patients treated from April 2021 onwards), Sensitivity #2 (incorporating day 0 ferritin and CRP values), and Sensitivity #3 (incorporating the maximum standardized uptake value from pre-CAR T positron emission tomography/computed tomography scans). Adjusted hazard ratios (HR) or odds ratios (OR) are displayed with 95% confidence intervals. Statistical significance is denoted as *P<0.05; **P<0.01; ***P<0.001. CAR: chimeric antigen receptor. axi-cel: axicabtagene ciloleucel; liso-cel: lisocabtagene maraleucel.

closely aligned with a MAIC analysis of clinical trial patients, with nearly identical HR (95% CI) for OS (IPTW aHR *vs*. MAIC HR=1.34 [95% CI: 0.73-2.47] *vs*. 1.23 [95% CI: 0.67-2.27]) and PFS (0.97 [95% CI: 0.60-1.56] *vs*. 0.93 [95% CI: 0.58-1.48]).[17] This reinforces the robustness of our real-world findings.

Safety is a critical factor in selecting CD19 CAR T-cell therapy, particularly for older or frail patients. In our analyses, axi-cel was associated with higher odds of any-grade and grade 2+ CRS, as well as any-grade ICANS, in both IPTW and unweighted MV regression models. These findings correlated with elevated peak inflammatory markers (i.e., CRP, ferritin, IL-6, D-dimer, ALT) observed in axi-cel patients. Moreover, a greater proportion of axi-cel patients required tocilizumab (55% *vs*. 32%) and dexamethasone (64% *vs*. 38%), reflecting a higher need for toxicity management. These results align with prior adjusted comparisons of axi-cel and liso-cel, which have also demonstrated significantly higher rates of CRS and neurologic toxicity in axi-cel recipients.[17,18] However, it is important to note that we did not observe significant differences in rates of grade 3+ CRS or ICANS - events that have the most substantial impact on morbidity and mortality - and rates of NRM were comparable.

We additionally observed more severe hematologic toxicity following axi-cel, with higher odds of any-grade and grade 2+ early ICAHT in both IPTW and unweighted MV regression analyses. Although a significantly higher proportion of axi-cel patients experienced grade 3+ early ICAHT, this finding was not statistically confirmed in our regression models. Several factors likely contribute to these observations. First, the higher cyclophosphamide dose used in the lymphodepletion regimen for axi-cel (500 mg/m^2/day for 3 days) compared to liso-cel (300 mg/m^2/day for 3 days) may play a significant role. Second, more pronounced systemic inflammation during CRS, as shown in our prior research,[28] likely exacerbates hematologic toxicity. Finally, the CD28 co-stimulatory domain in axi-cel, known to induce greater toxicity compared to the 4-1BB domain used in liso-cel,[29] may further explain the differences in toxicity profiles.

This study has several limitations that should be considered when interpreting the findings. First, its retrospective design is inherently vulnerable to treatment allocation bias. To mitigate this, we applied IPTW and utilized MV models to reduce bias and improve the accuracy of our estimates. Nevertheless, residual confounding may still exist due to unmeasured factors such as physician preference, frailty, and total metabolic tumor volume. Sensitivity analyses incorporating baseline inflammatory markers (ferritin and CRP) and maximum SUV supported the findings of the primary analysis. However, the absence of standardized frailty assessments may have led to an underestimation of frailty in liso-cel recipients, despite no significant differences in HCT-CI or ECOG performance status scores between groups. Second, the earlier approval of axi-cel resulted in longer follow-up for axi-cel patients and a greater proportion treated in an earlier era, which could have influenced outcomes. Third, this was a single-center study, which may limit the generalizability of the findings to other centers. While a multi-center study could enhance statistical power and broaden applicability, it would likely introduce additional sources of confounding due to variations in practice patterns, patient populations, and data collection methods. Furthermore, logistical challenges, such as obtaining longitudinal laboratory data across multiple sites, may hinder the feasibility of achieving the same level of detail. Finally, while we could not detect an independent impact of CAR T-cell product type on efficacy, the relatively broad 95% CI of our IPTW estimates suggest the study may have been underpowered to detect small effect sizes. Larger studies with more comprehensive follow-up, narrower CI, and the inclusion of multi-center data will be essential to confirm these findings and provide greater generalizability.

To address the potential bias introduced by treatment era, we conducted a sensitivity analysis restricted to patients treated contemporaneously with liso-cel or axi-cel between April 2021 and May 2024. This analysis confirmed no significant differences in survival outcomes between the two products, supporting the conclusions of our primary analysis. Additionally, axi-cel remained associated with higher rates of CRS and ICANS. Importantly, no significant association was observed between product type and early ICAHT in the sensitivity analysis. However, it is noteworthy that axi-cel patients treated during this period received significantly more G-CSF compared to both liso-cel patients and axi-cel patients treated in earlier years. This increased G-CSF use among contemporaneous axi-cel patients may have masked an intrinsic product-related difference in the risk of early ICAHT.

In summary, our analysis, which applied IPTW to address treatment allocation bias and incorporated MV adjustments for additional confounders, found no evidence that CD19 CAR T-cell product type independently influenced efficacy outcomes in a relatively large cohort of LBCL patients treated with liso-cel or axi-cel in a real-world, non-trial setting with extended follow-up. However, liso-cel demonstrated a significantly lower incidence and severity of CRS and early ICAHT, as well as a reduced incidence of ICANS, highlighting its more favorable safety profile compared to axi-cel. Notably, rates of NRM were similar between the two products, highlighting the need for personalized treatment decisions. Our analysis demonstrates liso-cel's more favorable safety profile, which should be a key consideration when choosing between liso-cel and axi-cel. However, further data are needed to confirm whether axi-cel and liso-cel achieve comparable long-term outcomes. The lower incidence and severity of CRS and early ICAHT, along with reduced rates of ICANS, position liso-cel as a preferred option for older, frail, or hematologically compromised patients. Additionally, the shorter hospital stays associated with liso-cel treatment enable outpatient management, significantly alleviating resource demands – an especially critical factor in re-

source-constrained environments. For high-risk subgroups, treatment decisions should be guided by patient-specific factors, such as tolerance for toxicity and logistical considerations, including the shorter vein-to-vein time offered by axi-cel. Ultimately, the choice of therapy must be individualized, taking into account patient performance status, treatment objectives, and institutional protocols.

Disclosures

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Contributions

AJP interpreted data and drafted the manuscript. JG conceived of the study, edited the manuscript, and provided critical oversight. JH abstracted chart data. ECL computed early ICAHT scores. QVW performed statistical analysis and provided statistical oversight. MT, AA, AVH, ELK, LI, CP, AKG, MS, BGT, FM, AGC, FO, RDC, RSB, YJ and DGM reviewed and edited the manuscript.

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Data-sharing statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

1. Neelapu SS, Jacobson CA, Ghobadi A, et al. Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma. Blood. 2023;141(19):2307-2315.
2. 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.
3. 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.
4. U.S. Food and Drug Administration. Juno Therapeutics Inc., a Bristol-Myers Squibb Company. Breyanzi (lisocabtagene maraleucel) [package insert]. Santa Bothell, WA. https://www.fda.gov/media/145711/download. Accessed March 4, 2025.
5. U.S. Food and Drug Administration. Kite Pharma, Inc. Yescarta (axicabtagene ciloleucel) [package insert]. Santa Monica, CA. https://www.fda.gov/media/108377/download. Accessed March 4, 2025.
6. U.S. Food and Drug Administration. Novartis Pharmaceuticals Corporation. Kymriah (tisagenlecleucel) [package insert]. East Hanover, NJ. https://www.fda.gov/media/107296/download. Accessed March 4, 2025.
7. European Medicines Agency. Yescarta (axicabtagene ciloleucel). https://www.ema.europa.eu/en/medicines/human/EPAR/yescarta. Accessed March 4, 2025.
8. European Medicines Agency. Breyanzi (lisocabtagene maraleucel). https://www.ema.europa.eu/en/medicines/human/EPAR/breyanzi. Accessed March 4, 2025.
9. European Medicines Agency. Kymriah (tisagenlecleucel). https://www.ema.europa.eu/en/medicines/human/EPAR/kymriah. Accessed March 4, 2025.
10. Bishop MR, Dickinson M, Purtill D, et al. Second-line tisagenlecleucel or standard care in aggressive B-cell lymphoma. N Engl J Med. 2022;386(7):629-639.
11. Gauthier J, Gazeau N, Hirayama AV, et al. Impact of CD19 CAR T-cell product type on outcomes in relapsed or refractory aggressive B-NHL. Blood. 2022;139(26):3722-3731.
12. Bachy E, Le Gouill S, Di Blasi R, et al. A real-world comparison of tisagenlecleucel and axicabtagene ciloleucel CAR T cells in relapsed or refractory diffuse large B cell lymphoma. Nat Med. 2022;28(10):2145-2154.
13. Sehgal A, Hoda D, Riedell PA, et al. Lisocabtagene maraleucel as second-line therapy in adults with relapsed or refractory large B-cell lymphoma who were not intended for haematopoietic

stem cell transplantation (PILOT): an open-label, phase 2 study. Lancet Oncol. 2022;23(8):1066-1077.
14. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020;396(10254):839-852.
15. Abramson JS, Palomba ML, Gordon LI, et al. Two-year follow-up of lisocabtagene maraleucel in relapsed or refractory large B-cell lymphoma in TRANSCEND NHL 001. Blood. 2024;143(5):404-416.
16. Smith SD, Reddy P, Sokolova A, et al. Eligibility for CAR T-cell therapy: an analysis of selection criteria and survival outcomes in chemorefractory DLBCL. Am J Hematol. 2019;94(4):E117-E116.
17. Maloney DG, Kuruvilla J, Liu FF, et al. Matching-adjusted indirect treatment comparison of liso-cel versus axi-cel in relapsed or refractory large B cell lymphoma. J Hematol Oncol. 2021;14(1):140.
18. Looka A, Qualls DA, Matthews D, et al. A real-world comparison of commercial-use axicabtagene ciloleucel and lisocabtagene maraleucel in large B-cell lymphoma. Blood Adv. 2025;9(3):455-462.
19. Team RC. R: A language and environment for statistical computing. 4.4.1. Vienna, Austria: R Foundation for Statistical Computing; 2024.
20. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med. 2015;34(28):3661-3679.
21. Rosenbaum PR. Model-based direct adjustment. J Am Stat Assoc. 1987;82(398):387-394.
22. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika. 1983;70(1):41-55.
23. Roddie C, Neill L, Osborne W, et al. Effective bridging therapy can improve CD19 CAR-T outcomes while maintaining safety in patients with large B-cell lymphoma. Blood Adv. 2023;7(12):2872-2883.
24. Epperla N, Feng L, Shah NN, et al. Outcomes of patients with secondary central nervous system lymphoma following CAR T-cell therapy: a multicenter cohort study. J Hematol Oncol. 2023;16(1):111.
25. Stuart EA. Matching methods for causal inference: a review and a look forward. Stat Sci. 2010;25(1):1-21.
26. Kamdar M, Solomon SR, Arnason J, et al. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial. Lancet. 2022;399(10343):2294-2308.
27. 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.
28. Juluri KR, Wu QV, Voutsinas J, et al. Severe cytokine release syndrome is associated with hematologic toxicity following CD19 CAR T-cell therapy. Blood Adv. 2022;6(7):2055-2068.
29. Cappell KM, Kochenderfer JN. A comparison of chimeric antigen receptors containing CD28 versus 4-1BB costimulatory domains. Nat Rev Clin Oncol. 2021;18(11):715-727.