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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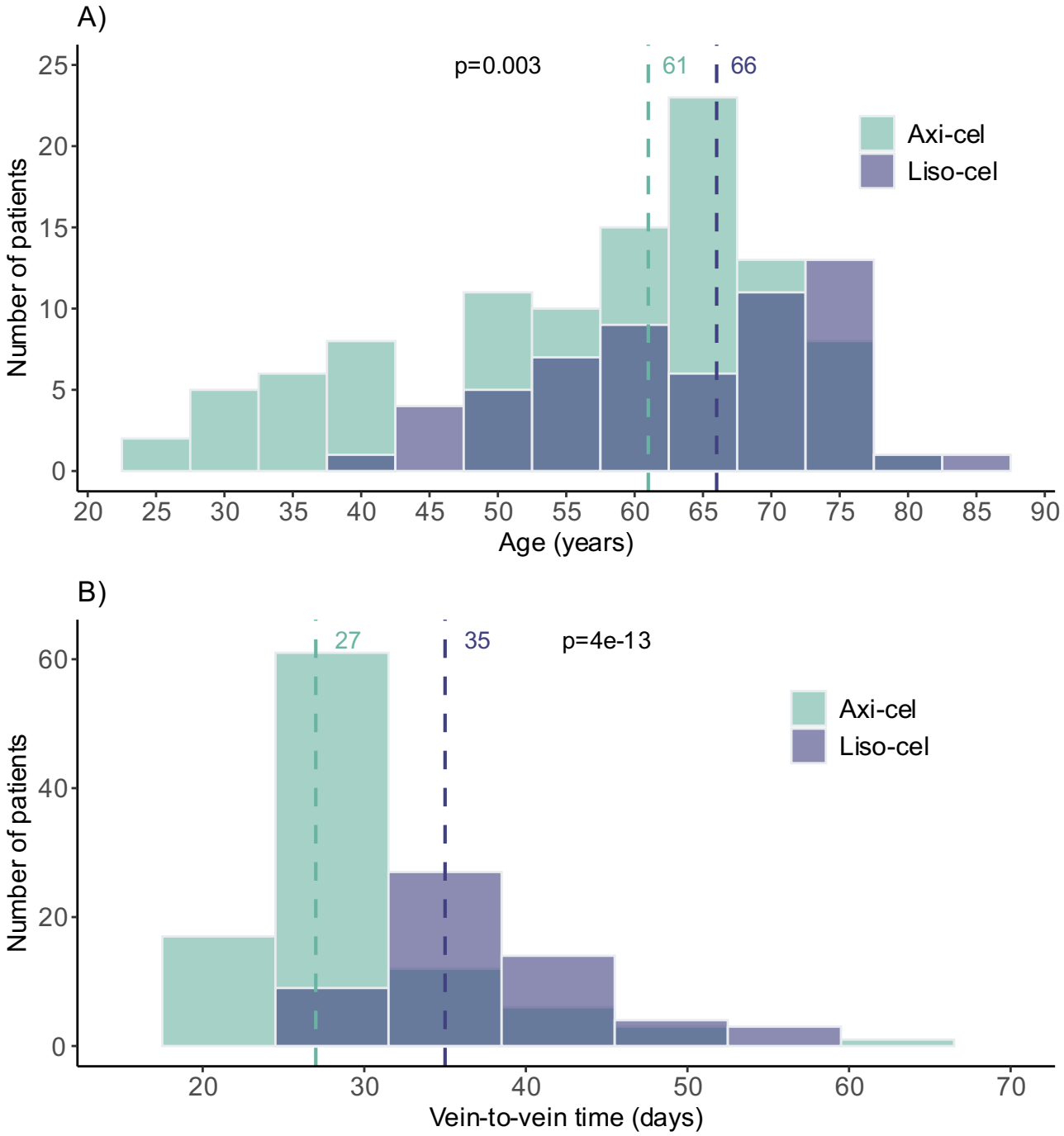
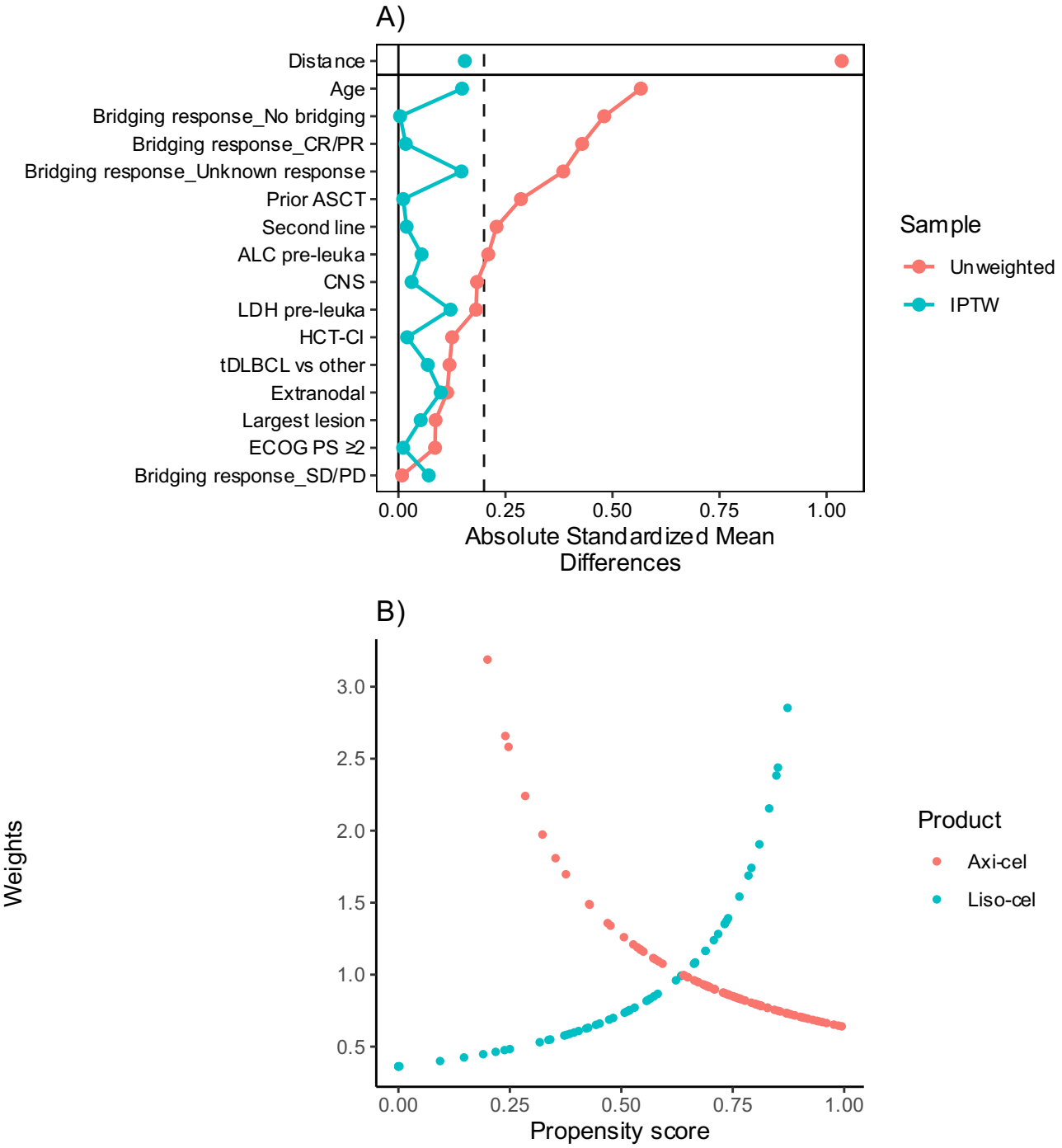
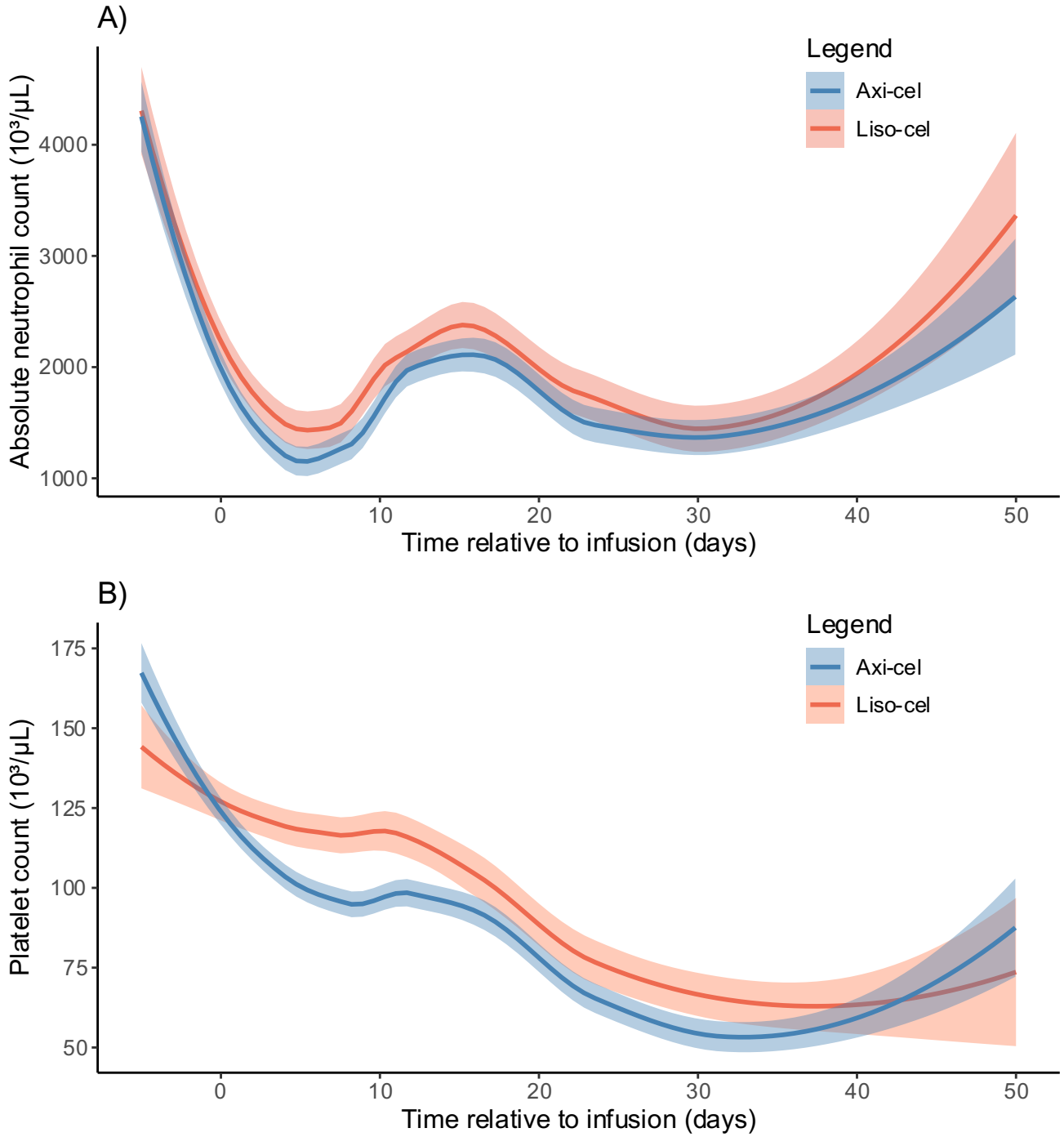
Supplemental Material for "Real-world comparison of lisocabtagene maraleucel and axicabtagene ciloleucel in large B-cell lymphoma: an inverse probability of treatment weighting analysis with 3-year follow up" by Portuguese et al.



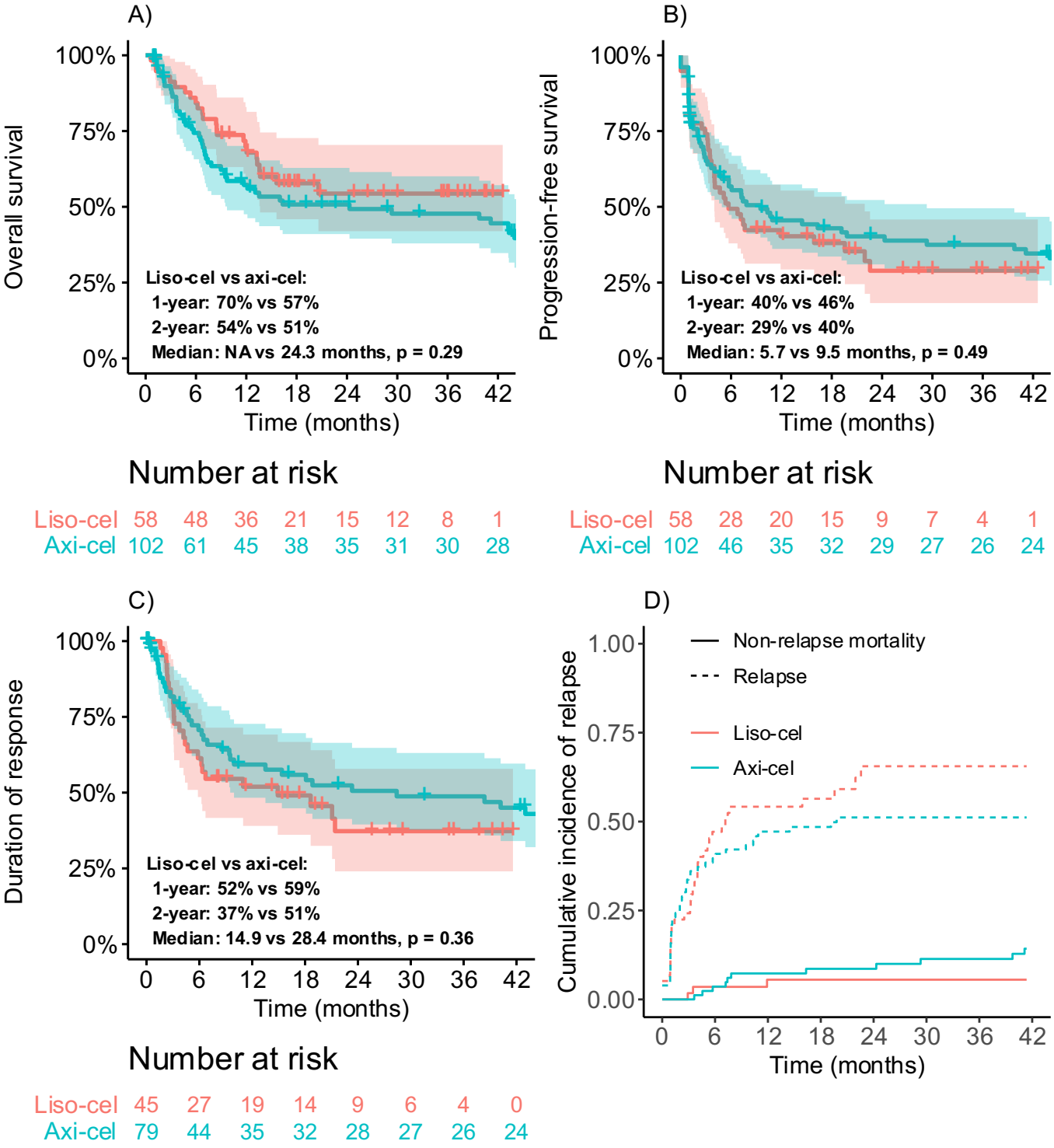
Supplemental Figure 1. Distribution of patient age and vein-to-vein time. Histograms depicting the distribution of A) age and B) time interval from apheresis to CAR-T product infusion ("vein-to-vein time"). Vertical dotted lines indicate median times. P values were derived from the Wilcoxon rank sum test



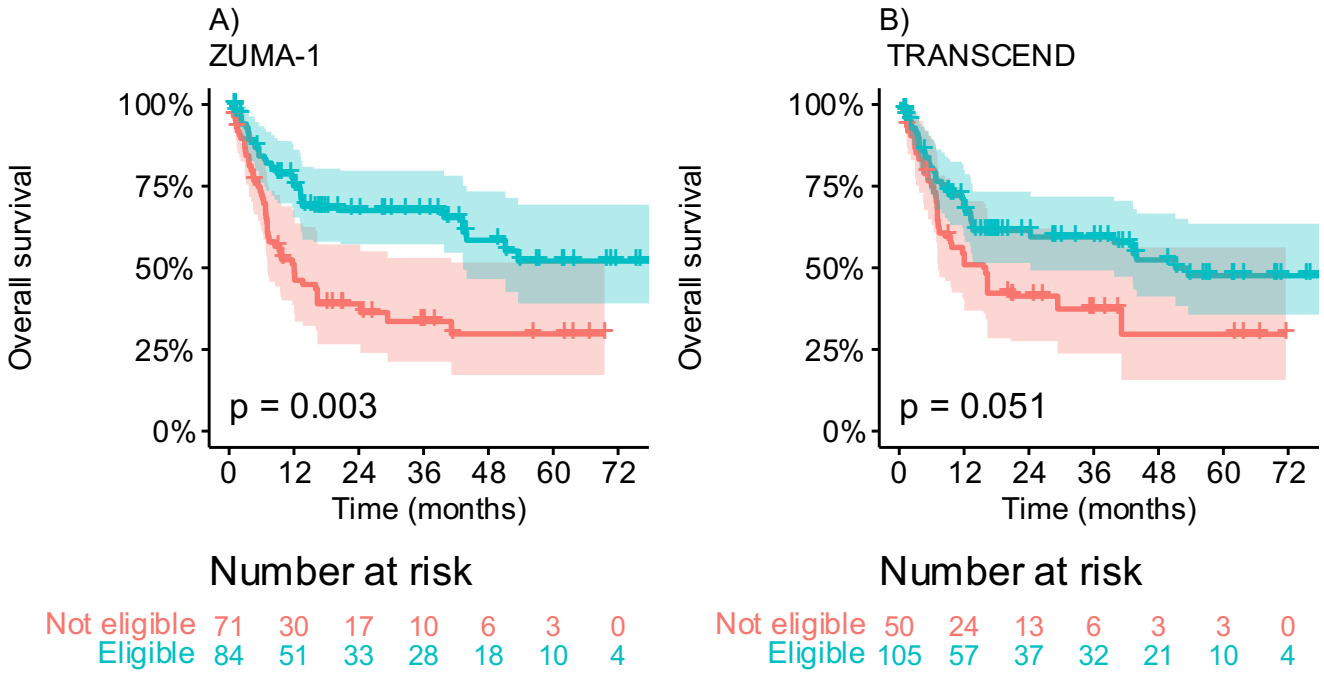
Supplemental Figure 2. Covariate balance and weight distribution in IPTW analysis. A) Love plot depicting covariate balance with and without inverse probability of treatment weighting (IPTW). The dotted line denotes an absolute standardized mean difference of 0.2. B) Scatterplot of assigned weights and propensity scores. ASCT = autologous hematopoietic stem cell transplantation; ALC = absolute lymphocyte count; LDH = lactate dehydrogenase; tDLBCL = transformed diffuse large B cell lymphoma; leuka = leukapheresis; ECOG PS = Eastern Cooperative Group performance status



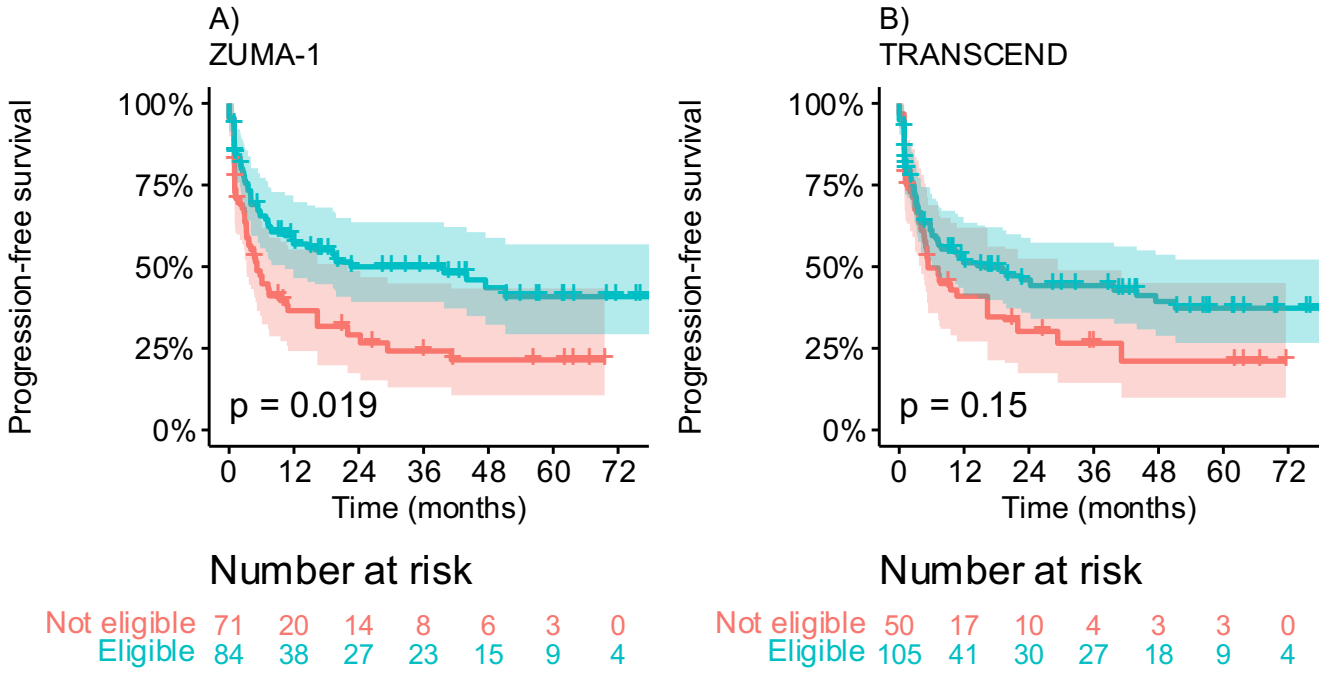
Supplemental Figure 3. Longitudinal trends in neutrophil and platelet counts. Unweighted longitudinal measurement of A) absolute neutrophil count and B) platelet. The lines represent LOESS-smoothed curves. Shaded areas around the curves denote 95% confidence intervals.



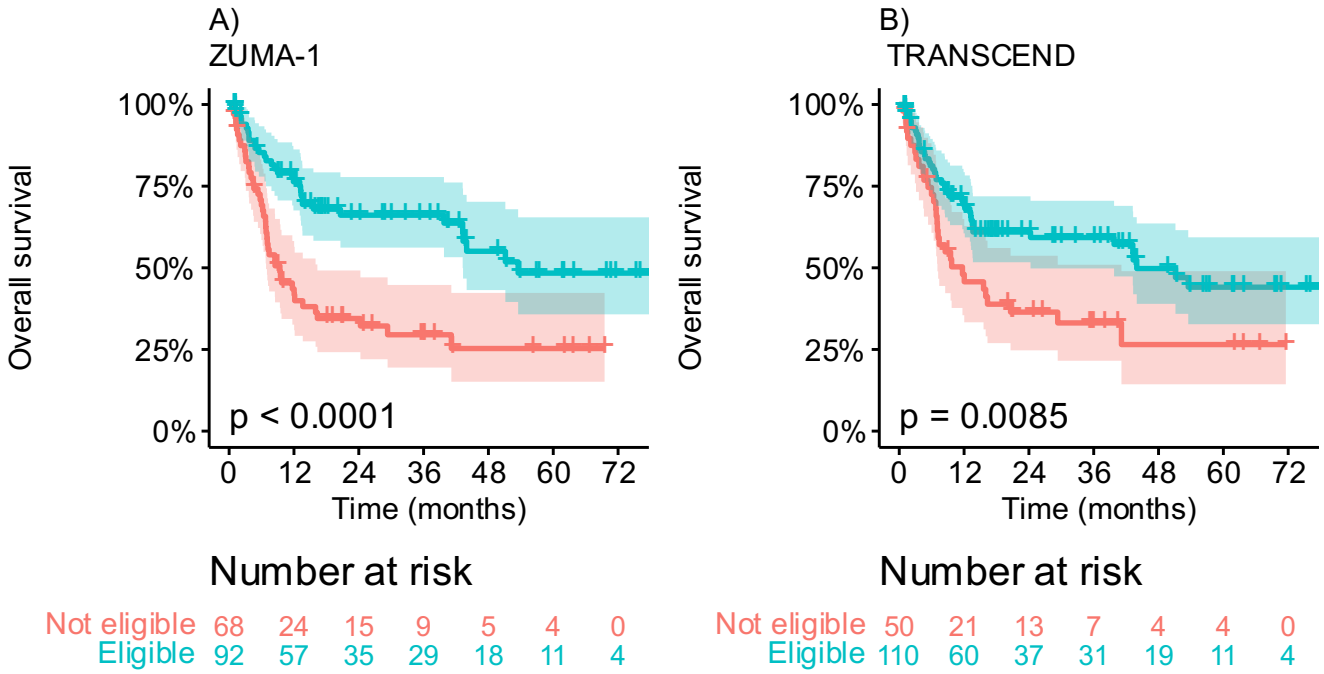
Supplemental Figure 4. Unweighed Kaplan-Meier analysis of survival outcomes by CAR-T product type. Unweighted Kaplan-Meier plots, stratified by CAR-T product type, depicting A) overall survival, B) progression-free survival, and C) cumulative incidence of relapse and non-relapse mortality. Median times were compared using the log rank test. Cumulative incidence curves for relapse were compared using Gray's test.



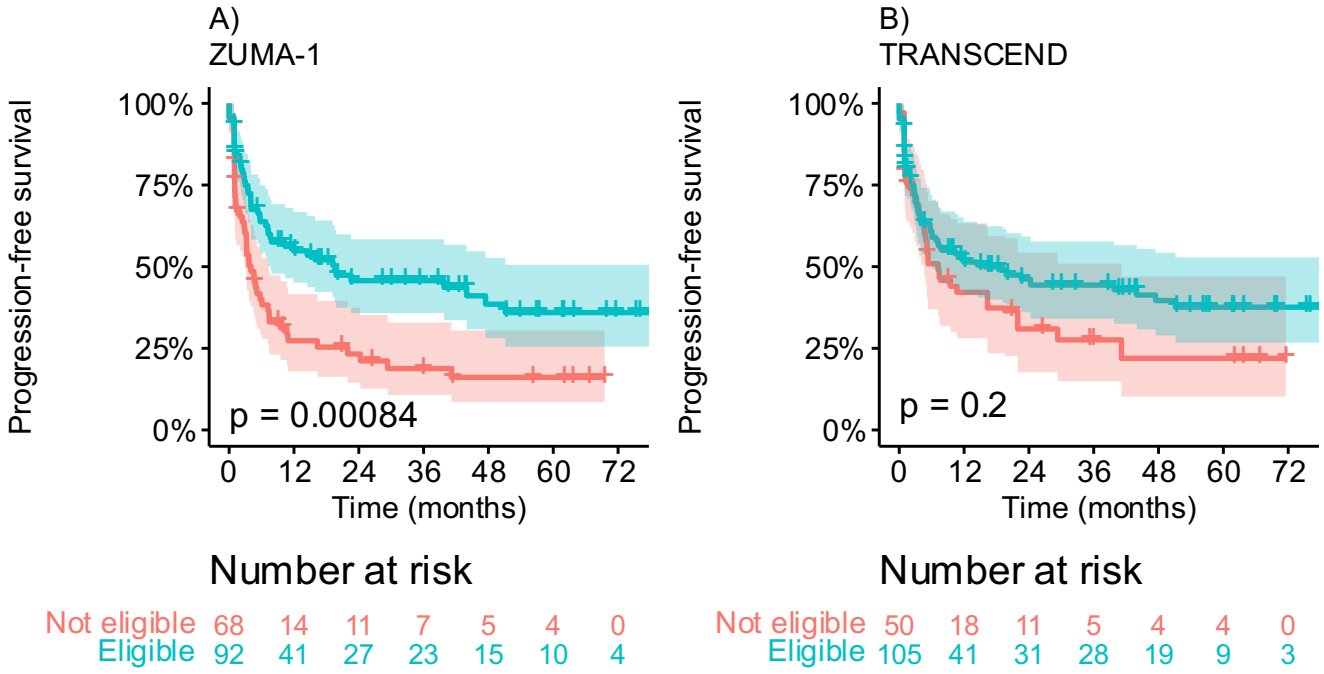
Supplemental Figure 5. IPTW Kaplan-Meier analysis of overall survival by eligibility criteria. IPTW Kaplan-Meier plots depicting overall survival, stratified by A) ZUMA-1 and B) TRANSCEND eligibility. P values were derived from weighted univariate Cox regression.



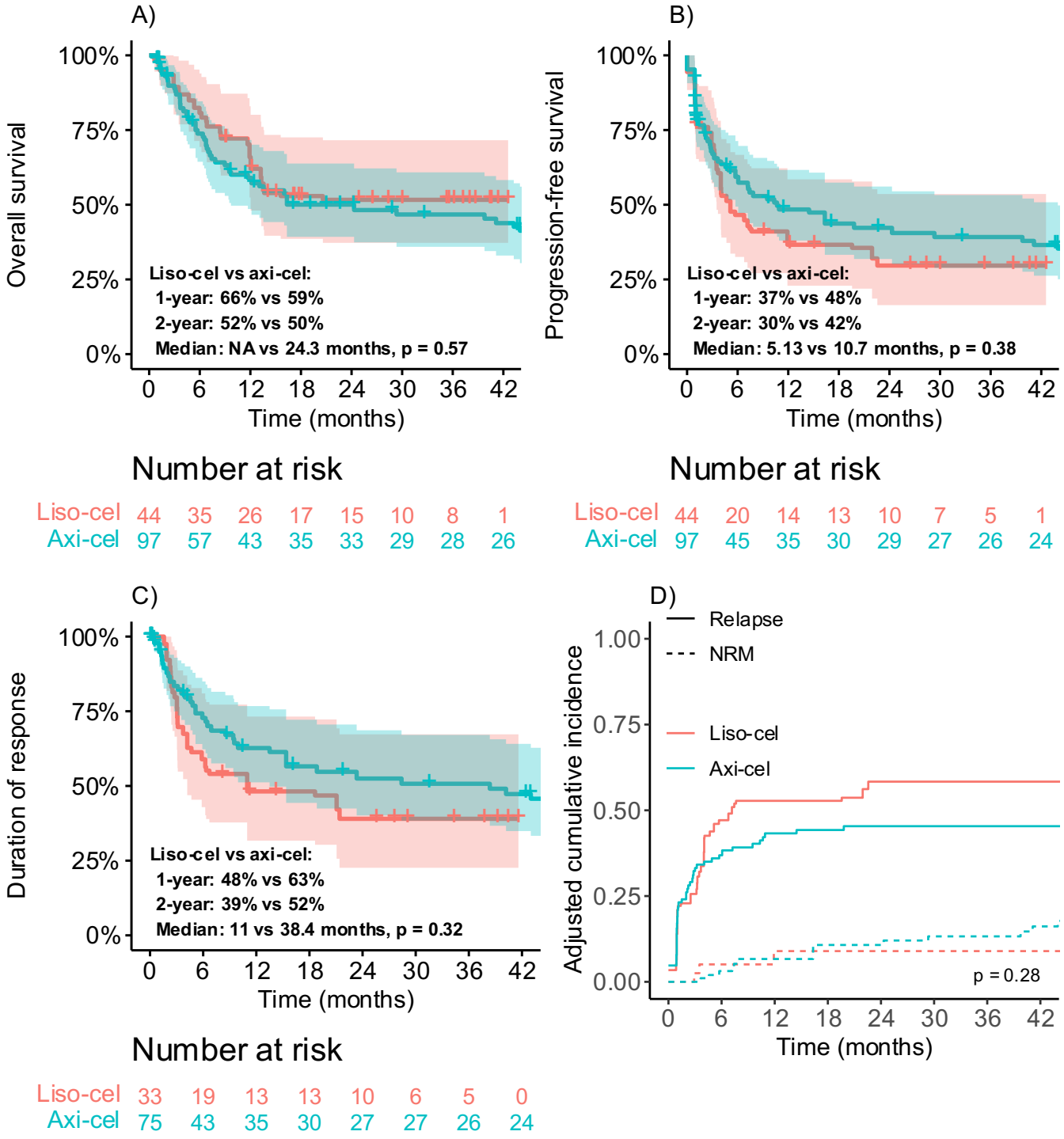
Supplemental Figure 6. IPTW Kaplan-Meier analysis of progression-free survival by eligibility criteria. IPTW Kaplan-Meier plots depicting progression-free survival, stratified by A) ZUMA-1 and B) TRANSCEND eligibility. P values were derived from weighted univariate Cox regression.



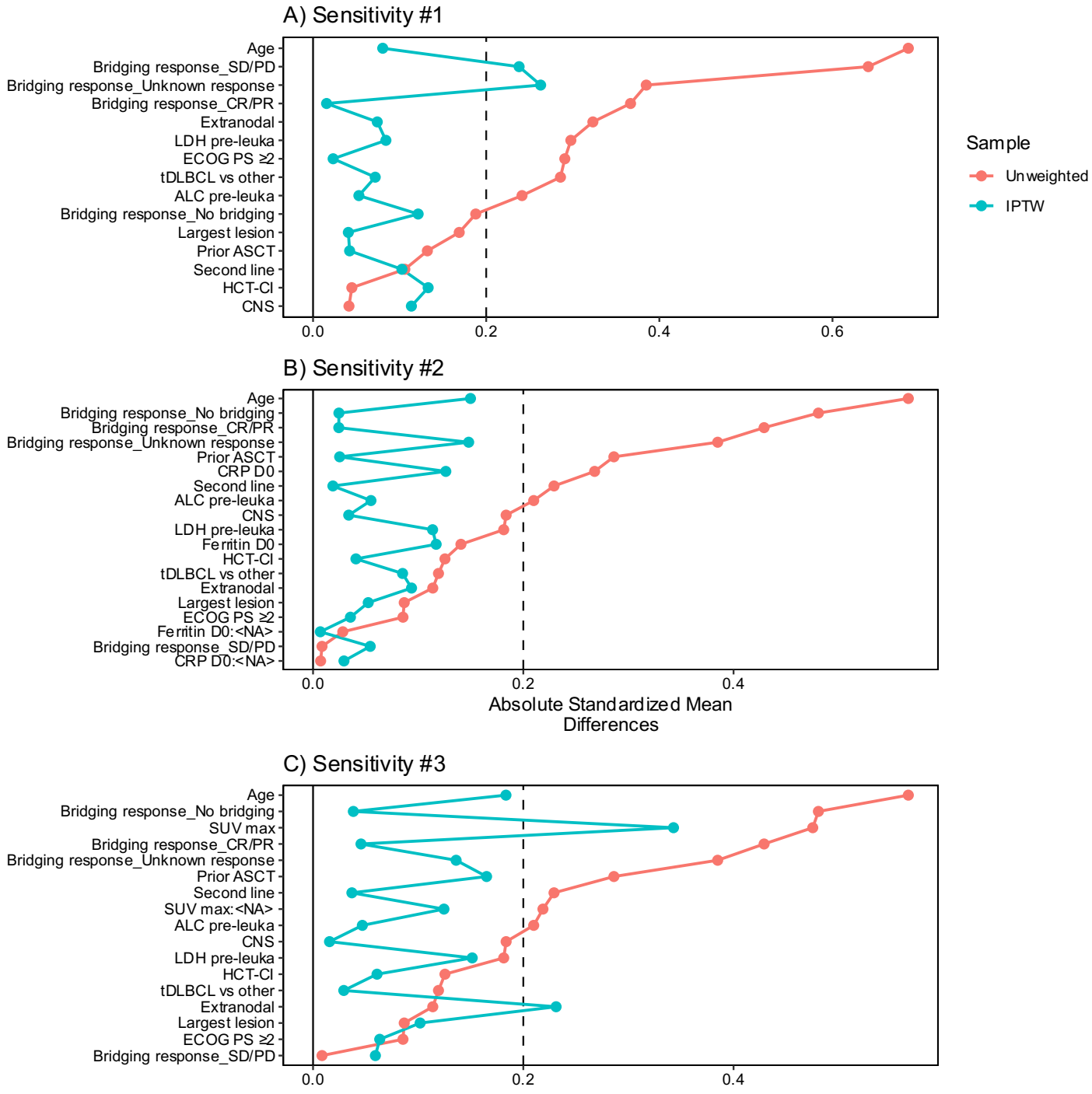
Supplemental Figure 7. Unweighted Kaplan-Meier analysis of overall survival by eligibility criteria. Unweighted Kaplan-Meier plots depicting overall survival, stratified by A) ZUMA-1 and B) TRANSCEND eligibility. P values were derived from the log-rank test.



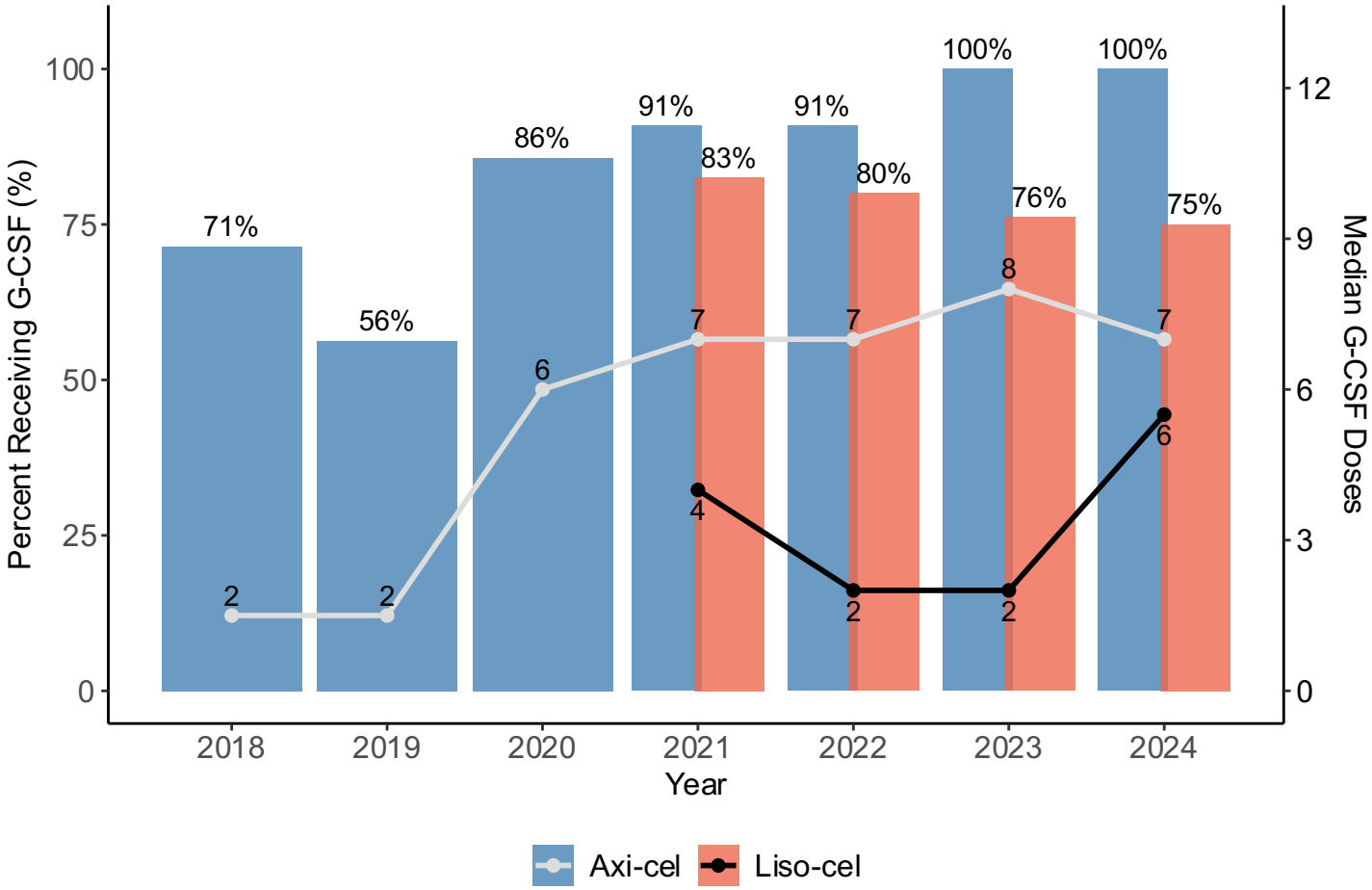
Supplemental Figure 8. Unweighted Kaplan-Meier analysis of progression-free survival by eligibility criteria. Unweighted Kaplan-Meier plots depicting progression-free survival, stratified by A) ZUMA-1 and B) TRANSCEND eligibility. P values were derived from the log-rank test.



Supplemental Figure 9. IPTW Kaplan-Meier analysis of outcomes among patients not in complete response at CAR-T infusion. IPTW Kaplan-Meier plots illustrating A) overall survival, B) progression-free survival, C) duration of response, and D) cumulative incidence of relapse and non-relapse mortality (NRM), among patients not in a complete response at the time of CAR-T infusion. Median survival times were analyzed using weighted univariate Cox regression, and the 1-year cumulative incidence of relapse was assessed with Gray's test.



Supplemental Figure 10. Love plots illustrating the absolute standardized mean differences for sensitivity analyses. A) Sensitivity #1 (restricted to patients treated from April 2021 onwards), B) Sensitivity #2 (incorporating day 0 ferritin and CRP values), and C) Sensitivity #3 (incorporating the maximum SUV from pre-CAR-T PET/CT scans). The dotted line represents a threshold of 0.2.



Supplemental Figure 11. Trends in granulocyte colony-stimulating factor (G-CSF) utilization over time. Annual utilization of G-CSF among patients receiving axi-cel and liso-cel, including the percentage of patients receiving G-CSF (bars) and the median number of doses (lines). Data are shown by year from 2018 to 2024, with distinct patterns in G-CSF use between the two CAR T-cell products, reflecting differences in treatment practices and dosing trends over time.

Supplemental Table 1. Unweighted and IPTW peak inflammatory markers after CAR T-cell infusion.

Characteristic	IPTW			Unweighted		
	Liso-cel N = 55	**Axi-cel** N = 100	**p-value**[1]	**Liso-cel** N = 58	**Axi-cel** N = 102	**p-value**[2]
ALT max, Median (IQR)	32 (22, 58)	51 (31, 79)	0.020	32 (23, 67)	56 (36, 87)	0.003
AST max, Median (IQR)	30 (26, 44)	35 (25, 60)	0.2	31 (24, 50)	37 (27, 63)	0.079
CRP max, Median (IQR)	71 (9, 125)	114 (56, 171)	0.002	68 (9, 123)	118 (58, 179)	<0.001
D-dimer max, Median (IQR)	1.3 (0.7, 3.3)	2.4 (1.4, 4.7)	0.011	1.3 (0.7, 3.2)	2.5 (1.6, 5.1)	<0.001
Ferritin max, Median (IQR)	666 (164, 1,692)	1,081 (436, 2,516)	0.009	783 (176, 1,786)	1,317 (488, 2,633)	0.007
IL6 max, Median (IQR)	55 (13, 665)	196 (57, 1,395)	0.030	56 (15, 477)	221 (62, 1,395)	<0.001
LDH max, Median (IQR)	212 (171, 328)	242 (174, 360)	0.3	215 (171, 357)	251 (191, 371)	0.10

[1] Design-based Kruskal-Wallis test
[2] Wilcoxon rank sum test

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRP = C-reactive protein; LDH = lactate dehydrogenase; IQR = interquartile range

Supplemental Table 2. Unweighted and IPTW infectious complications and treatment.

Characteristic	IPTW			Unweighted		
	Liso-cel N = 55	**Axi-cel** N = 100	**p-value**[1]	**Liso-cel** N = 58	**Axi-cel** N = 102	**p-value**[2]
Positive BCx, n (%)	2 (3.6%)	8 (8.3%)	0.3	2 (3.4%)	9 (8.8%)	0.3
Positive CMV, n (%)	18 (32%)	28 (28%)	0.6	17 (29%)	31 (30%)	0.9
CMV requiring treatment, n (%)	4 (7.5%)	6 (5.8%)	0.7	5 (8.6%)	6 (5.9%)	0.5
CMV duration, Median (IQR)	15 (0, 23)	17 (7, 34)	0.5	19 (0, 23)	17 (7, 34)	0.4
Cefepime doses, Median (IQR)	0 (0, 9)	8 (0, 15)	0.004	0 (0, 8)	9 (0, 16)	<0.001
Received cefepime, n (%)	23 (43%)	71 (71%)	0.003	24 (41%)	72 (71%)	<0.001
Vancomycin doses, Median (IQR)	0.0 (0.0, 1.0)	0.0 (0.0, 2.0)	>0.9	0.0 (0.0, 0.0)	0.0 (0.0, 4.0)	0.2
Received vancomycin, n (%)	15 (28%)	27 (27%)	0.9	13 (22%)	32 (31%)	0.2
Received norepinephrine, n (%)	2 (4.4%)	1 (0.9%)	0.15	2 (3.4%)	1 (1.0%)	0.3

[1] Pearson's X^2: Rao & Scott adjustment; Design-based Kruskal-Wallis test
[2] Fisher's exact test; Pearson's Chi-squared test; Wilcoxon rank sum test

BCx = blood culture; CMV = cytomegalovirus; IQR = interquartile range

Supplemental Table 3. Summary of unweighted univariate and multivariable regression.

			Univariate			Multivariable		
			OR	**95% CI**	**p-value**	**aOR**	**95% CI**	**p-value**
CR	**Product**	Liso-cel	—	—		—	—	
		Axi-cel	1.27	0.63, 2.54	0.5	1.3	0.55, 3.08	0.5
	Pre-leuka LDH		0.15	0.03, 0.62	0.009	0.17	0.03, 0.87	0.033
	Pre-leuka ALC		2.24	1.09, 4.63	0.029	2.33	1.02, 5.32	0.045
	Largest lesion		0.89	0.80, 0.99	0.026	0.96	0.85, 1.09	0.5
			HR	**95% CI**	**p-value**	**aHR**	**95% CI**	**p-value**
DOR	**Product**	Liso-cel	—	—		—	—	
		Axi-cel	0.78	0.46, 1.32	0.4	0.78	0.41, 1.48	0.4
	Pre-leuka LDH		5.93	2.24, 15.7	<0.001	4.2	1.33, 13.3	0.015
	Pre-leuka ALC		0.65	0.34, 1.24	0.2	0.79	0.45, 1.40	0.4
	Largest lesion		1.08	1.00, 1.15	0.046	0.99	0.90, 1.10	>0.9
			HR	**95% CI**	**p-value**	**aHR**	**95% CI**	**p-value**
Relapse	**Product**	Liso-cel	—	—		—	—	
		Axi-cel	0.79	0.51, 1.22	0.3	0.83	0.50, 1.37	0.5
	Pre-leuka LDH		2.49	1.22, 5.05	0.012	1.53	0.66, 3.52	0.3
	Pre-leuka ALC		0.75	0.45, 1.23	0.3	0.86	0.61, 1.21	0.4
	Largest lesion		1.08	1.02, 1.15	0.007	1.02	0.94, 1.09	0.7
			HR	**95% CI**	**p-value**	**aHR**	**95% CI**	**p-value**
PFS	**Product**	Liso-cel	—	—		—	—	
		Axi-cel	0.87	0.57, 1.31	0.5	0.86	0.54, 1.39	0.5
	Pre-leuka LDH		3.17	1.68, 5.97	<0.001	1.94	0.92, 4.11	0.082
	Pre-leuka ALC		0.67	0.41, 1.11	0.12	0.83	0.56, 1.22	0.3
	Largest lesion		1.1	1.04, 1.16	<0.001	1.03	0.96, 1.10	0.4
			HR	**95% CI**	**p-value**	**aHR**	**95% CI**	**p-value**
OS	**Product**	Liso-cel	—	—		—	—	
		Axi-cel	1.31	0.79, 2.15	0.3	1.23	0.67, 2.25	0.5
	Pre-leuka LDH		8.89	4.07, 19.4	<0.001	3.84	1.48, 9.91	0.006
	Pre-leuka ALC		0.75	0.44, 1.28	0.3	0.85	0.53, 1.36	0.5
	Largest lesion		1.15	1.09, 1.22	<0.001	1.07	0.99, 1.15	0.078
			OR	**95% CI**	**p-value**	**aOR**	**95% CI**	**p-value**
CRS, any grade	**Product**	Liso-cel	—	—		—	—	
		Axi-cel	5.22	2.24, 12.1	<0.001	4.67	1.60, 13.7	0.005
	Pre-leuka LDH		28.7	2.60, 316	0.006	57.9	2.54, 1,318	0.011
	Pre-leuka ALC		1.21	0.61, 2.41	0.6	1.51	0.54, 4.21	0.4
	Largest lesion		1.28	1.08, 1.51	0.005	1.28	1.04, 1.58	0.022
			OR	**95% CI**	**p-value**	**aOR**	**95% CI**	**p-value**
CRS, grade 2+	**Product**	Liso-cel	—	—		—	—	
		Axi-cel	3.46	1.67, 7.18	<0.001	3.2	1.39, 7.34	0.006
	Pre-leuka LDH		3.37	0.99, 11.4	0.051	2.45	0.60, 10.0	0.2
	Pre-leuka ALC		0.89	0.62, 1.28	0.5	0.9	0.62, 1.29	0.6
	Largest lesion		1.05	0.96, 1.15	0.3	1.03	0.92, 1.15	0.6
			OR	**95% CI**	**p-value**	**aOR**	**95% CI**	**p-value**
ICANS, any grade	**Product**	Liso-cel	—	—		—	—	
		Axi-cel	2.81	1.43, 5.56	0.003	2.52	1.07, 5.93	0.034
	Pre-leuka LDH		14.3	3.20, 63.9	<0.001	8.67	1.68, 44.8	0.01
	Pre-leuka ALC		0.91	0.67, 1.24	0.6	0.97	0.66, 1.43	0.9
	Largest lesion		1.18	1.07, 1.31	0.001	1.17	1.03, 1.32	0.014
			OR	**95% CI**	**p-value**	**aOR**	**95% CI**	**p-value**
Early ICAHT, any grade	**Product**	Liso-cel	—	—		—	—	
		Axi-cel	4.1	1.62, 10.4	0.003	7.53	2.19, 25.8	0.001
	Pre-leuka LDH		137	5.31, 3,548	0.003	25.1	0.45, 1,405	0.12
	Pre-leuka ALC		1.1	0.62, 1.95	0.7	1.2	0.48, 2.99	0.7
	Largest lesion		1.27	1.05, 1.54	0.015	1.07	0.83, 1.39	0.6
			OR	**95% CI**	**p-value**	**aOR**	**95% CI**	**p-value**
Early ICAHT, grade 2+	**Product**	Liso-cel	—	—		—	—	
		Axi-cel	4.62	2.16, 9.91	<0.001	4.21	1.72, 10.3	0.002
	Pre-leuka LDH		5.23	1.44, 19.0	0.012	4.15	0.91, 18.9	0.065
	Pre-leuka ALC		0.82	0.50, 1.35	0.4	0.78	0.37, 1.64	0.5
	Largest lesion		1.08	0.99, 1.18	0.1	1.06	0.94, 1.19	0.3

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 10^3 cells/μL, and the size of the largest lesion was measured in 1 cm units.

Supplementary Methods

Definitions

LBCLs were categorized according to the 5th edition of the World Health Organization classification of hematolymphoid tumors: lymphoid neoplasms.(1) Treatment response was assessed via Positron Emission Tomography and Computed Tomography (PET-CT) scan per the Lugano 2014 criteria.(2) Patients were considered response-evaluable if they had measurable FDG-avid disease (Deauville 4 or 5) by PET-CT after bridging chemotherapy, when applicable, and prior to the start of lymphodepletion chemotherapy.

Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded using American Society for Transplantation and Cellular Therapy (ASTCT) criteria.(3) Notably, patients who experienced neurotoxicity prior to 2019 (n=11) were originally graded using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0(4) and subsequently re-classified using the ASTCT criteria. Early immune effector cell-associated hematotoxicity (ICAHT; day 0-30) was graded according to the European Hematology Association and European Society for Blood and Marrow Transplantation as previously described.(5) Fever and neutropenia were defined as a body temperature ≥38 °C and an ANC $<0.5 \times 10^9$/L, respectively.

The number of admissions and total inpatient duration were calculated as the number of admissions and number of days requiring hospital admission from the day of infusion through day +30, respectively. Patients given axi-cel were required to remain inpatient for a minimum of 7 days following CAR T-cell infusion per the FDA package insert. Bridging therapy was defined as lymphoma-directed therapy administered post-leukapheresis, excluding corticosteroids and external beam radiation therapy. Prophylactic dexamethasone was defined as once-daily dexamethasone 10 mg on day 0 (before CAR T-cell infusion) through day 2.(6)

Granulocyte colony-stimulating factor (G-CSF) was administered per institutional practice for patients with an ANC <1,000/mm³. G-CSF utilization was calculated based on the total number of doses administered from the day of infusion through day +30.

Inverse probability of treatment weighting (IPTW)

Multivariable (MV) analysis adjusts for confounding by including covariates directly within a regression model, thereby accounting for the influence of multiple confounders simultaneously. However, MV analysis does not explicitly address the probability of treatment allocation, potentially leaving residual confounding. To mitigate bias related to treatment allocation, several advanced methods are available, including Inverse Probability of Treatment Weighting (IPTW), Matching-Adjusted Indirect Comparison (MAIC), and propensity score (PS) matching.

IPTW uses the inverse of the propensity score (the probability of receiving a specific treatment) to generate a weighted pseudo-population in which covariates between treated and untreated groups are balanced. This enables the estimation of treatment effects as though treatment were randomly assigned. Unlike PS matching, which excludes unmatched participants, IPTW includes all participants in the analysis by applying weights, thereby preserving statistical power. It provides an unbiased estimate of the average treatment effect (ATE) across the entire target population by effectively addressing confounding variables.(7-9)

MAIC is primarily used to compare outcomes between studies with different patient populations. It adjusts individual-level patient data from one study to align with the aggregate characteristics of patients in another study. MAIC is typically employed when individual patient data (IPD) are available for one study but only summary-level data are available for the comparator study.(10) In our case, MAIC was not necessary, as we had access to individual patient data for both treatment groups.

PS matching attempts to create comparable treatment and control groups by matching participants based on their propensity scores. This method reduces confounding by retaining only matched pairs for analysis. However, PS matching can lead to the exclusion of unmatched participants, reducing the sample size and limiting the generalizability of the findings to the matched population only.(11-14)

We chose IPTW for our analysis because it retains the full sample, preserving statistical power and producing more generalizable results applicable to the overall population. This approach offers a favorable balance between bias reduction and the maintenance of statistical robustness.

IPTW MV regression models included the following covariates: CAR T-cell product type (liso-cel vs. axi-cel; binary), pre-leukapheresis LDH (U/L; continuous), pre-leukapheresis ALC (10^3/μL; continuous), and largest lesion diameter (cm; continuous). Unweighted MV regression models utilized the same covariates which were included for IPTW: pre-leukapheresis LDH (U/L; continuous), pre-leukapheresis ALC (10^3/μL; continuous), age (years; continuous), prior autologous HCT (binary), use of CAR T-cell therapy in the 2nd line setting (binary), ECOG performance status ≥2 (binary), transformed LBCL vs. other (binary), largest lesion diameter (cm; continuous), presence of non-CNS extranodal disease (binary), the presence of CNS involvement (binary), HCT-CI score (continuous), and bridging response category (as described above).

IPTW was conducted using the *WeightIt* (version 1.3.0) package.(15) Propensity scores were estimated using logistic regression, and stabilized inverse probability of treatment weights were calculated per best practices to preserve sample size and provide accurate variance estimations.(7, 16) Weighted cumulative incidence curves were generated using the *adjustedCurves* package (Version 0.11.2) with the IPTW method.(17)

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