Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about the work.

Tisagenlecleucel Versus Standard of Care in Second-Line Aggressive B-Cell Lymphoma

Table of Contents

Investigator List

Last Name	First Name	Country	Patients?
Rabitsch	Werner	Austria	
Greil	Richard	Austria	
Rudzki	Jakob	Austria	None
Thieblemont	Catherine	France	
Bachy	Emmanuel	France	
Morschhauser	Franck	France	
Gastinne	Thomas	France	
Cartron	Guillaume	France	
Ysebaert	Loic	France	
Borchmann	Peter	Germany	
Dreyling	Martin	Germany	
Viardot	Andreas	Germany	
Janz	Martin	Germany	
Ayuketang Ayuk	Francis	Germany	
Thomas	Simone	Germany	
Vucinic	Vladan	Germany	
Corradini	Paolo	Italy	
Sica	Simona	Italy	
Santoro	Armando	Italy	
Mueller	Antonia	Switzerland	
Kersten	M.J.	Netherlands	
Minnema	M.C.	Netherlands	
Ardeshna	Kirit	United Kingdom	
Chaganti	Sridhar	United Kingdom	
Holte	Harald	Norway	
Beguin	Yves	Belgium	None (closed site)
Vandenberghe	Peter	Belgium	
Sureda Balari	Anna	Spain	
Martinez Lopez	Joaquin	Spain	
Barba Sunol	Pere	Spain	
Kwon	Mi	Spain	
Garcia Sancho	Alejandro	Spain	
Dickinson	Michael	Australia	
Hamad	Nada	Australia	
Purtill	Duncan	Australia	
KWONG	Yok-lam	Hong Kong	
Hwang	William	Singapore	
Chan	Hian Li Esther	Singapore	
Yao	Ming	Taiwan, Republic of China	
Hamerschlak	Nelson	Brazil	

Last Name	First Name	Country	Patients?
Salvino Araujo	Marco Aurelio	Brazil	
Holmes	Houston	United States	
Cohen	Jonathon	United States	
Deol	Abinav	United States	
Westin	Jason	United States	
Mulroney	Carolyn	United States	
Flinn	Ian	United States	
Mead	Monica	United States	
Maziarz	Richard	United States	
Bishop	Michael	United States	
McGuirk	Joseph	United States	
Bond	David	United States	
Schuster	Stephen	United States	
Kenkre	Vaishalee	United States	
Andreadis	Charalambos	United States	
McSweeney	Peter	United States	
Vose	Julie	United States	
Kharfan Dabaja	Mohamed	United States	
Hess	Brian	United States	
Shaughnessy	Paul	United States	
Essell	James	United States	
Leslie	Lori	United States	
Ramakrishnan	Aravind	United States	
Teshima	Takanori	Japan	
Harigae	Hideo	Japan	
Kato	Koji	Japan	
Song	Yuqin	China	
Jing	Hongmei	China	
Qian	Wenbin	China	None
Niu	Ting	China	None
Li	Lanfang	China	None
Li	Yuhua	China	None
Yang	Haiyan	China	None
Li	Ping	China	
Huang	He	China	None
Xia	Ruixiang	China	None
Sang	Wei	China	None

SUPPLEMENTARY FIGURES
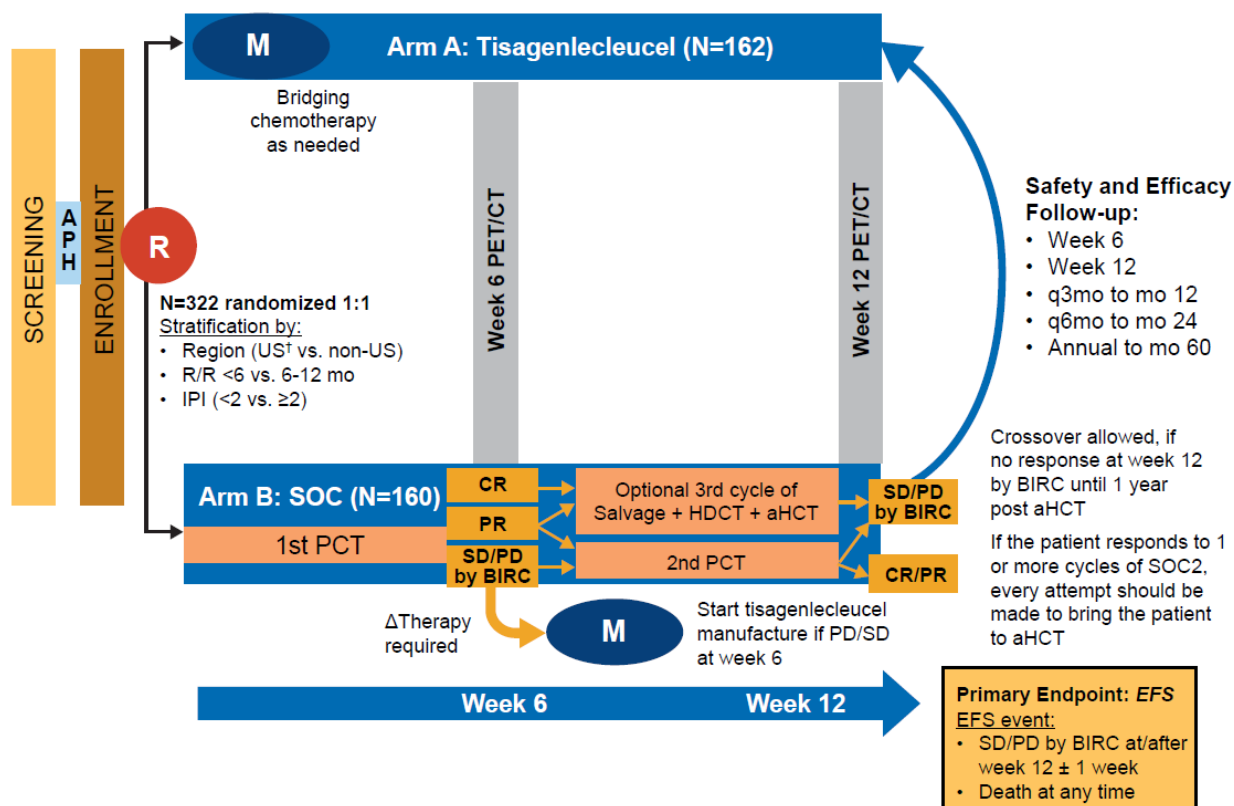
Figure S1. BELINDA Study Design.

Note: Sample sizes indicate expected numbers and not the final design.

aHCT denotes autologous hematopoietic stem cell transplantation, APH leukapheresis, BIRC blinded independent review committee, CR complete response, CT computed tomography, EFS event-free survival, HDCT high-dose chemotherapy, IPI International Prognostic Index, M manufacturing, PCT platinum-based immunochemotherapy, PD progressive disease, PET positron emission tomography, PR partial response, q3mo every 3 months, q6mo every 6 months, R randomization, R/R relapsed or refractory, SD stable disease, SOC standard of care, and US United States.
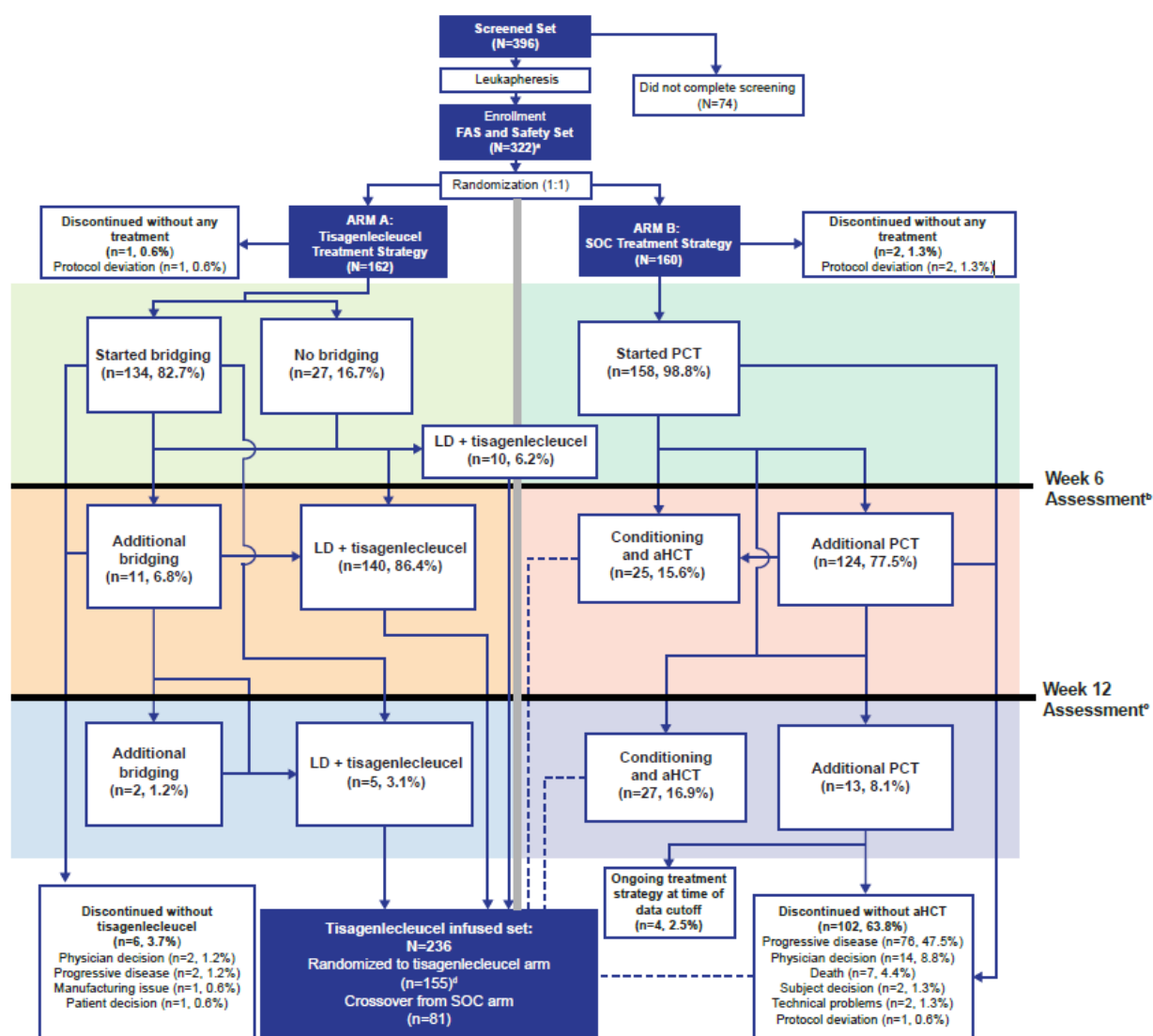
Figure S2. CONSORT Diagram.

Dashed lines indicate crossover.

[a]Full analysis and safety sets used to compare efficacy and safety between the 2 treatment strategies. [b]Week 6 assessment is the earliest disease assessment on or after day 29 and on or before day 70. [c]Week 12 assessment is the earliest disease assessment on or after day 71.

[d]Tisagenlecleucel-infused set used to assess efficacy and safety of tisagenlecleucel in second-line therapy (tisagenlecleucel arm) and third-line therapy (crossover).

aHCT denotes autologous hematopoietic stem cell transplantation, FAS full analysis set, LD lymphodepletion chemotherapy, PCT platinum-based immunochemotherapy, and SOC standard of care.

A) Tisagenlecleucel Arm
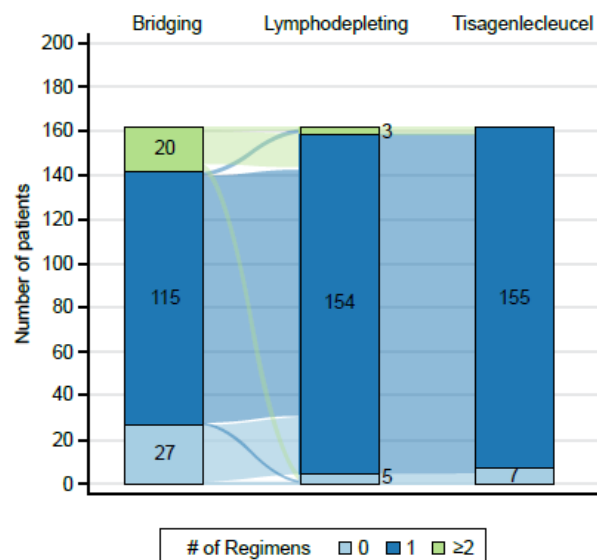
B) SOC Arm
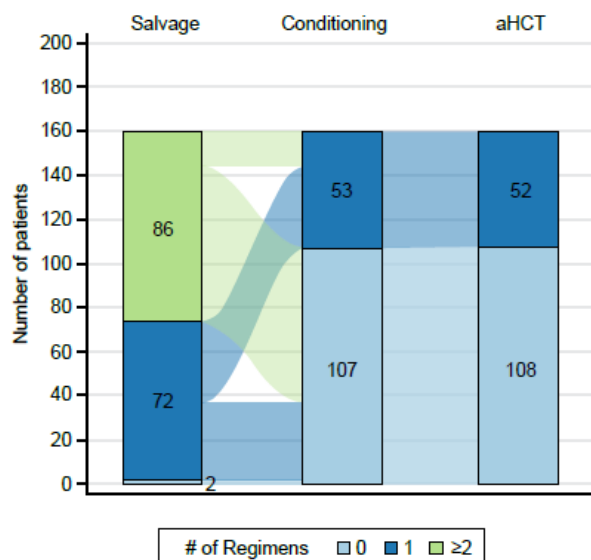
C) Treatments Received in Tisagenlecleucel Treatment Strategy (N=162)
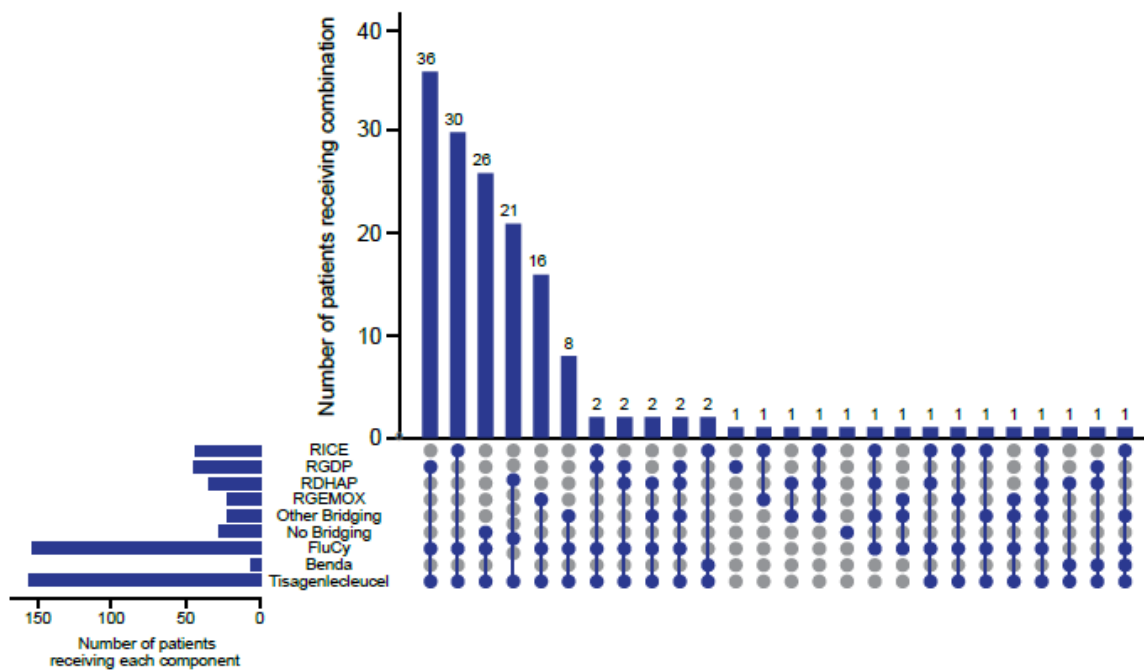
D) Treatments Received in SOC Treatment Strategy (N=160)
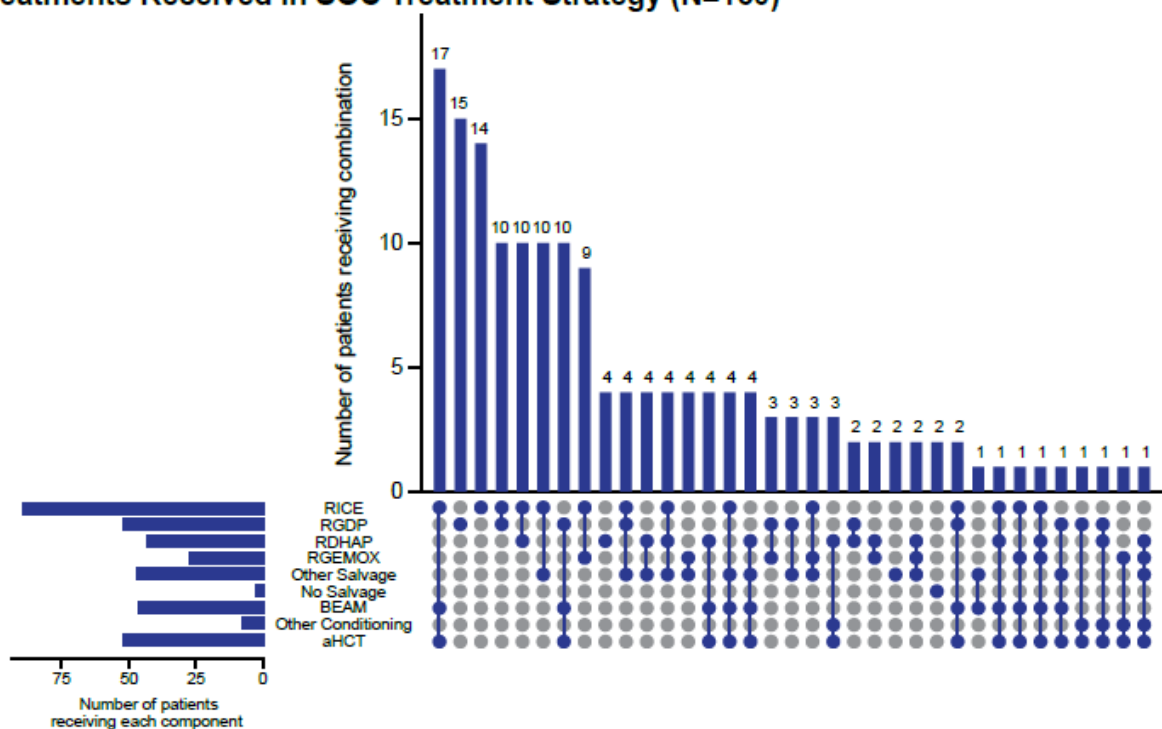
Figure S3. Treatment Strategies Received per Treatment Arm.

In panel C, 1 patient started Flu/Cy, which was interrupted after 1 day for disease progression, and a few days later received 2 days of bendamustine before being infused with tisagenlecleucel.

aHCT denotes autologous hematopoietic stem cell transplantation; BEAM carmustine, etoposide, cytarabine, and melphalan; Benda bendamustine; Flu/Cy fludarabine and cyclophosphamide; RDHAP rituximab, dexamethasone, cytarabine, and cisplatin; RGDP rituximab, gemcitabine, dexamethasone, and cisplatin; RGEMOX rituximab, gemcitabine, and oxaliplatin; RICE rituximab, ifosfamide, carboplatin, and etoposide; and SOC standard of care.
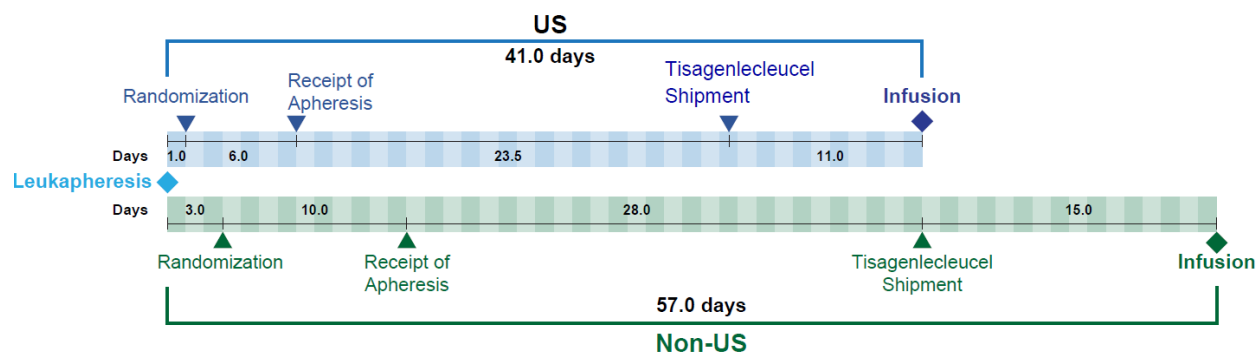
Figure S4. Median Time for Different Steps from Leukapheresis to Tisagenlecleucel Infusion.

Leukapheresis was performed during screening.
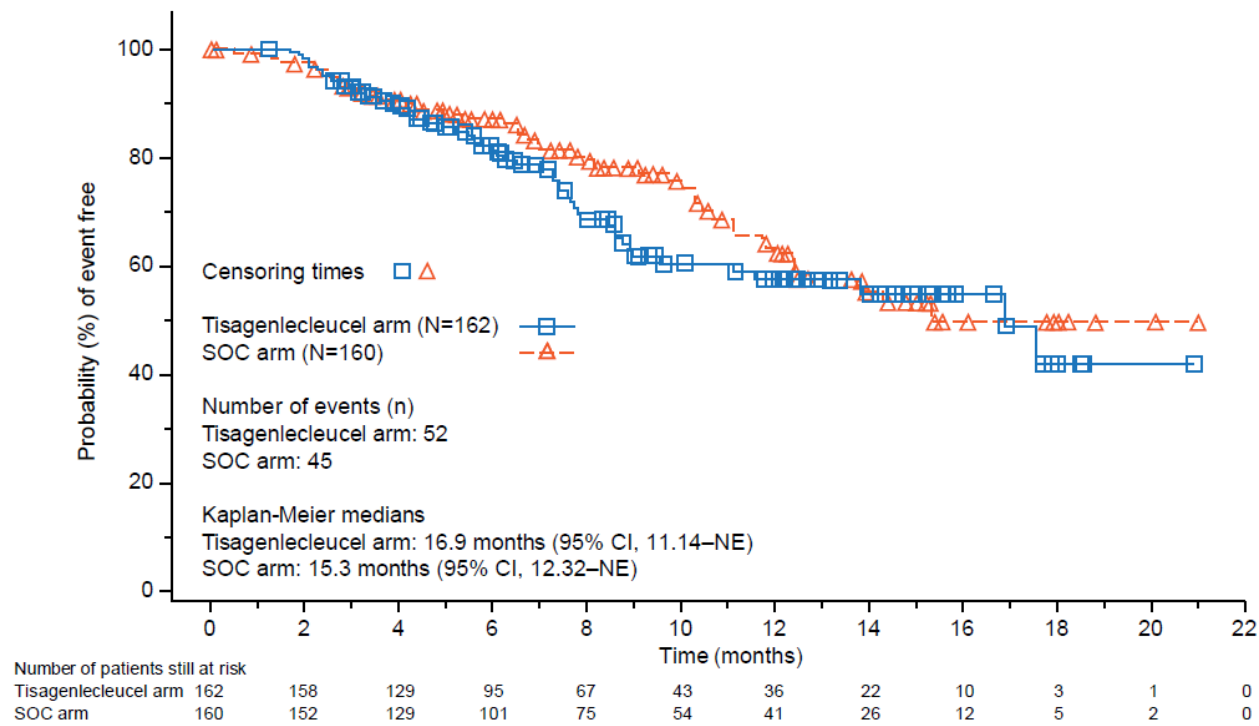
Figure S5. Kaplan-Meier Plot of OS.

OS events defined as the time from date of randomization to date of death due to any cause.

CI denotes confidence interval, NE not estimable, OS overall survival, and SOC standard of care.

A)

B)

C)

Censoring times △ □ ◇ ○
DLBCL NOS (N=101) ——△——
PMBCL (N=12) ——□——
HBGL (N=39) ---◇---
Other (N=10) ——○——

Number of events (n)
DLBCL NOS: 24
PMBCL: 0
HBGL: 25
Other: 3

Kaplan-Meier medians
DLBCL NOS: NE months (95% CI, 11.6–NE)
PMBCL: NE months (95% CI, NE–NE)
HBGL: 7.7 months (95% CI, 4.6–11.1)
Other: 16.9 months (95% CI, 2.2–NE)
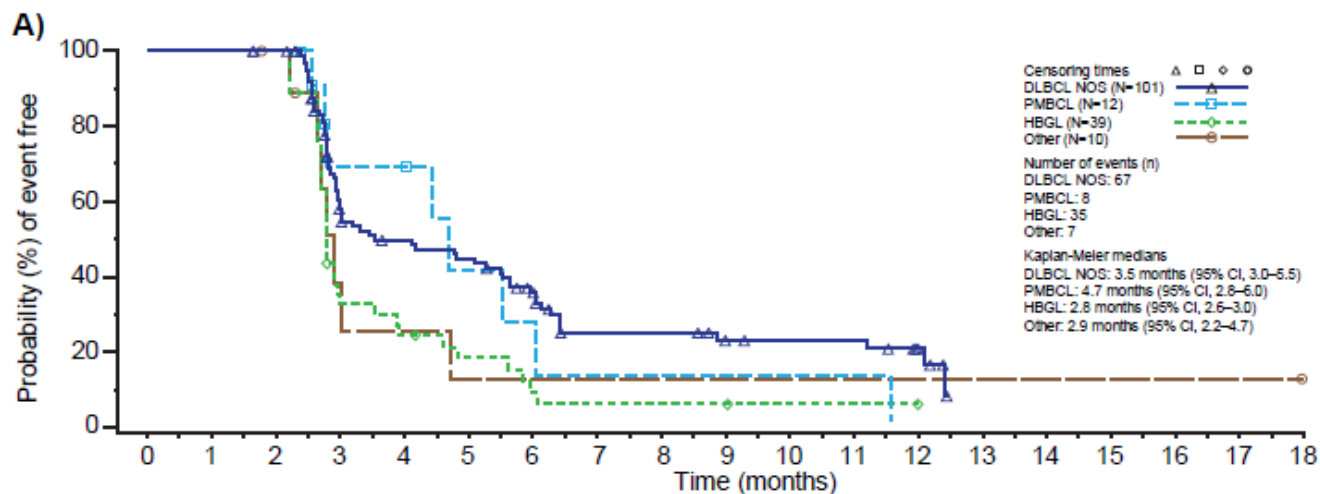
No. of patients still at risk
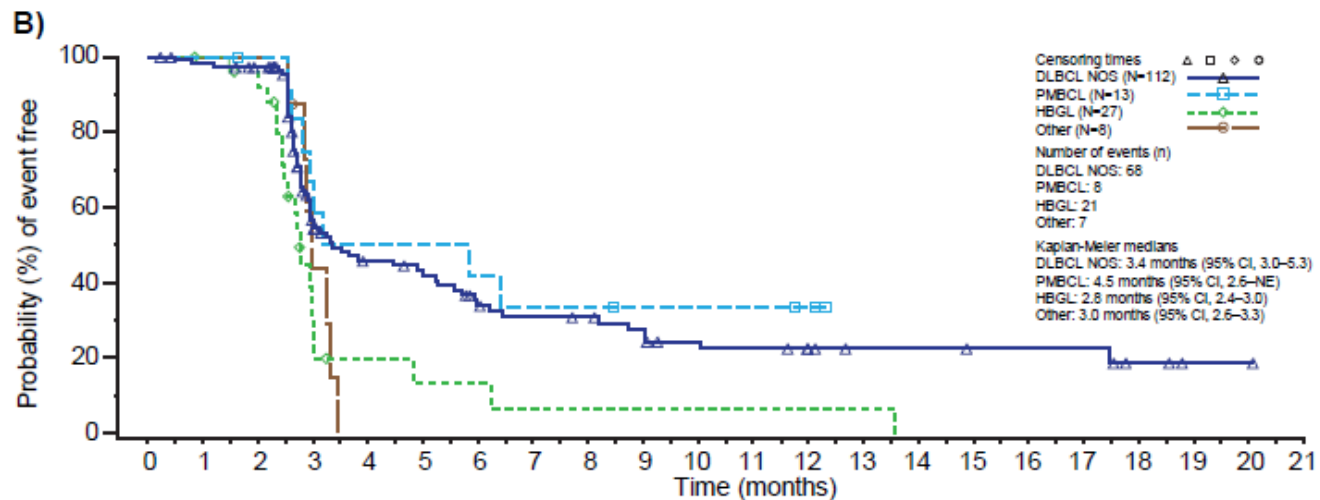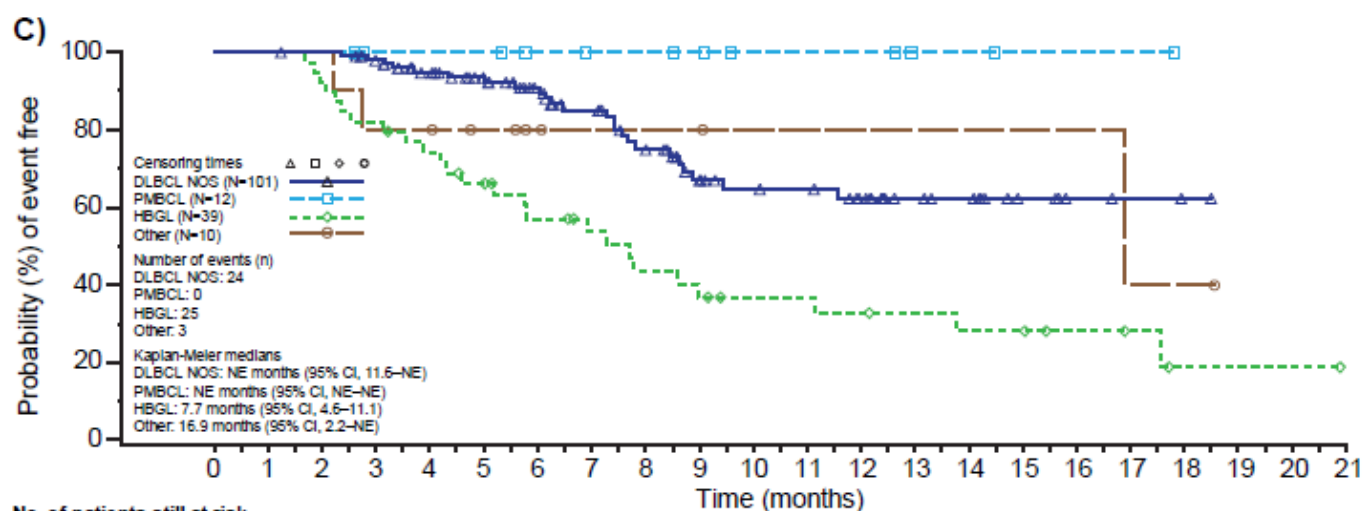
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
DLBCL NOS	101	101	100	94	83	74	64	54	44	33	28	27	22	14	12	6	3	2	1	0	0	0
PMBCL	12	12	12	10	10	10	8	7	7	6	4	4	4	2	2	1	1	1	0	0	0	0
HBGL	39	39	36	32	28	24	19	16	13	11	9	9	8	7	6	6	4	3	1	1	1	0
Other	10	10	10	8	8	6	4	3	3	3	2	2	2	2	2	2	2	1	1	0	0	0

D)

Censoring times △ □ ◇ ○
DLBCL NOS (N=112) ——△——
PMBCL (N=13) ——□——
HBGL (N=27) ---◇---
Other (N=8) ——○——

Number of events (n)
DLBCL NOS: 24
PMBCL: 2
HBGL: 15
Other: 4

Kaplan-Meier medians
DLBCL NOS: NE months (95% CI, 12.4–NE)
PMBCL: 15.3 months (95% CI, 15.3–NE)
HBGL: 7.1 months (95% CI, 3.8–13.9)
Other: 7.9 months (95% CI, 2.9–NE)

No. of patients still at risk
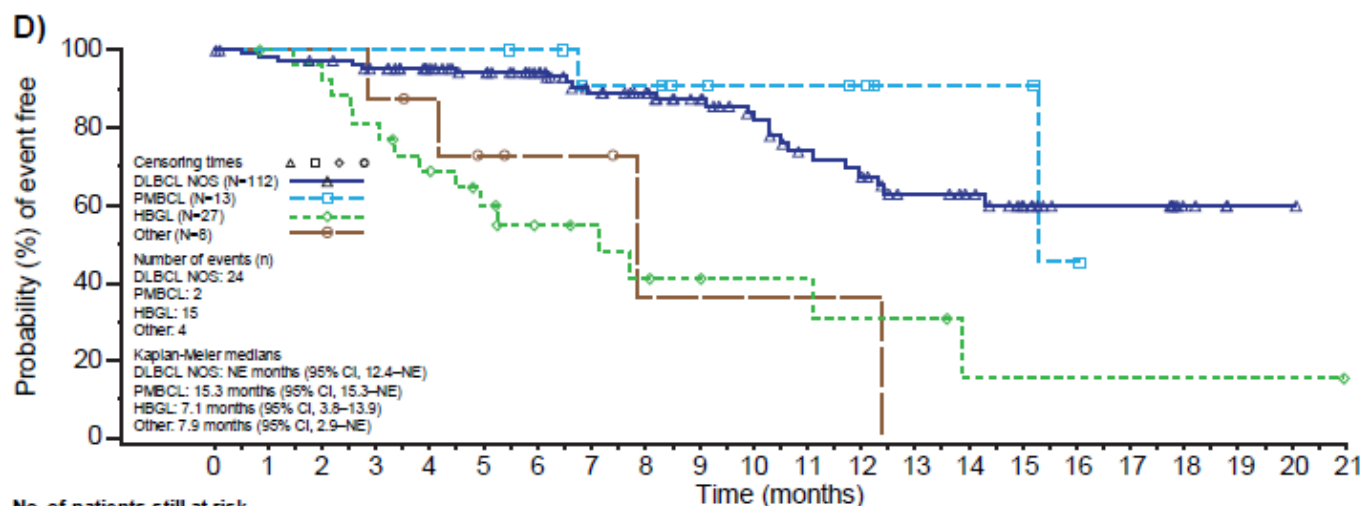
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
DLBCL NOS	112	108	106	101	93	86	77	64	59	51	43	35	32	25	22	16	10	10	4	1	1	0
PMBCL	13	13	13	13	13	13	12	9	9	7	6	6	5	3	3	3	1	0	0	0	0	0
HBGL	27	26	25	21	17	13	9	8	6	5	4	4	3	3	1	1	1	1	1	1	1	0
Other	8	8	8	7	6	4	3	3	1	1	1	1	1	0	0	0	0	0	0	0	0	0

Figure S6. Kaplan-Meier Plots of EFS per BIRC and OS in Tisagenlecleucel and SOC Arms by Disease Diagnosis.

EFS events defined as PD/SD after day 71 or death at any time (i.e., EFS at a given timepoint represents the estimated proportion of responders at this timepoint among all randomized patients). OS events defined as the time from date of randomization to date of death due to any cause. **A)** EFS per BIRC in the tisagenlecleucel arm. **B)** EFS per BIRC in the SOC arm. **C)** OS in the tisagenlecleucel arm. **D)** OS in the SOC arm.

BIRC denotes blinded independent review committee, CI confidence interval, DLBCL NOS diffuse large B-cell lymphoma not otherwise specified, EFS event-free survival, HGBL high-grade B-cell lymphoma, NE not estimable, OS overall survival, PD progressive disease, PMBCL primary mediastinal B-cell lymphoma, SD stable disease, and SOC standard of care.

Secondary Endpoints (Overall Survival and Best Overall Response)

Overall survival is defined as the time from date of randomization to date of death due to any cause. All deaths occurring on or before the cutoff date were used in the overall survival analysis. If a patient was not known to have died by the data cutoff date, overall survival was censored at the date of last contact.

The overall response rate is defined as the proportion of subjects with a best overall response of complete or partial response according to Lugano criteria. Best overall response is defined as the best overall disease response from the sequence of overall disease responses observed between the week 12 assessment and the first to occur between the data cutoff date, start date of a new anticancer therapy, and date of an event-free survival event. That is, response assessments before the week 12 assessment are not used in the calculation of best overall response in order to maintain consistency with the definition of event-free survival used in this study. For example, a patient with an overall disease response of progressive disease at week 6 followed by complete response at week 12 would have a best overall response of complete response. Response assessments as early as week 10 (study day 71) will be considered as valid week 12 assessments. A separate definition "best overall response post-infusion" will also be used in the tisagenlecleucel infused set. This refers to the best overall disease response considering efficacy assessments post-infusion and before the data cutoff date, start date of a new anticancer therapy, and date of progressive disease.

Post-hoc Exploratory Variable Selection for Multivariate Modeling

To assess the relationship between disease characteristics and status before infusion, use of bridging, and CAR-T cell dose on post-infusion modified best overall response and modified event-free survival, 15 variables including potential confounders were initially identified as candidate covariates by drawing a directed acyclic graph (this was formed from an

assessment of potential confounders and possible causal relationships based on clinical considerations). In addition, variable clustering analysis (https://support.sas.com/resources/papers/proceedings/proceedings/sugi26/p261-26.pdf) using $1-R^2$ ratio as assessment criteria to remove redundant variables from each cluster was conducted to reduce the dimension and select the final set of covariates used to build the multivariate models. As a result, the covariates selected include CAR-T cell dose, region, bridging cycles, sex, Eastern Cooperative Oncology Group performance status, disease subtypes, remission duration, International Prognostic Index score, and response status before infusion.

Post-hoc Exploratory Multivariate Logistic Regression Model for Post-infusion Modified Best Overall Response in Arm A

As a post-hoc exploratory analysis, a multivariate logistic regression for post-infusion modified best overall response (complete or partial response vs stable disease/partial disease/unknown) was fitted based on the 9 covariates identified from the variable selection step. An interaction term for dose and response status before infusion was added to the model. The results in Table S7 showed that the odds ratio estimate was 7.75 with 95% confidence interval (CI), 3.23–18.62, for patients in complete or partial response before infusion compared to patients in stable or progressive disease pre-infusion. In addition, the estimated odds ratio for dose was 1.61 with 95% CI, 0.98–2.63, in patients in stable or progressive disease before infusion and was 0.93 with 95% CI, 0.51–1.70, in patients in complete or partial response before infusion.

Post-hoc Exploratory Multivariate Cox Regression Model for Post-infusion Modified Event-free Survival in Arm A

A multivariate Cox regression for post-infusion modified event-free survival was also fitted based on the 9 covariates and an interaction term for dose and response status before infusion. The model results (Table S6) showed an HR of 2.30 (95% CI, 1.44–3.66) in patients with stable or progressive disease before infusion compared to patients who were in complete or partial response status before infusion. The Cox model for modified event-free survival also estimated the HR of dose was 0.73 (95% CI, 0.57–0.93) for patients in stable or progressive disease before infusion and was 1.26 (95% CI, 0.91–1.73) for patients in complete or partial response before infusion.

Subgroup	Events/N (%)	Median Time (95% CI) (months)	Stratified Cox model HR (95% CI)
Histology			
DLBCL NOS			
Tisagenlecleucel arm	67/101 (66.3)	3.5 (3.0–5.5)	
SOC arm	68/112 (60.7)	3.4 (3.0–5.3)	
PMBCL			
Tisagenlecleucel arm	8/12 (66.7)	4.7 (2.8–6.0)	
SOC arm	8/13 (61.5)	4.5 (2.6–NE)	
HGBL			
Tisagenlecleucel arm	35/39 (89.7)	2.8 (2.6–3.0)	
SOC arm	21/27 (77.8)	2.8 (2.4–3.0)	
Other			
Tisagenlecleucel arm	7/10 (70.0)	2.9 (2.2–4.7)	
SOC arm	7/ 8 (87.5)	3.0 (2.6–3.3)	
Molecular DLBCL cell of origin			
GCB			
Tisagenlecleucel arm	29/46 (63.0)	4.2 (2.8–5.9)	
SOC arm	41/63 (65.1)	3.0 (2.8–3.8)	
Non-GCB			
Tisagenlecleucel arm	35/52 (67.3)	4.1 (2.9–6.0)	
SOC arm	25/43 (58.1)	4.5 (2.9–9.0)	

0.25 0.5 1 2 4

Figure S7. EFS per BIRC by Diagnosis of Disease.

BIRC denotes blinded independent review committee, CI confidence interval, DLBCL NOS diffuse large B-cell lymphoma not otherwise specified, EFS event-free survival, GCB germinal center B-cell, HGBL high-grade B-cell lymphoma, HR hazard ratio, NE not estimable, PMBCL primary mediastinal B-cell lymphoma, and SOC standard of care.
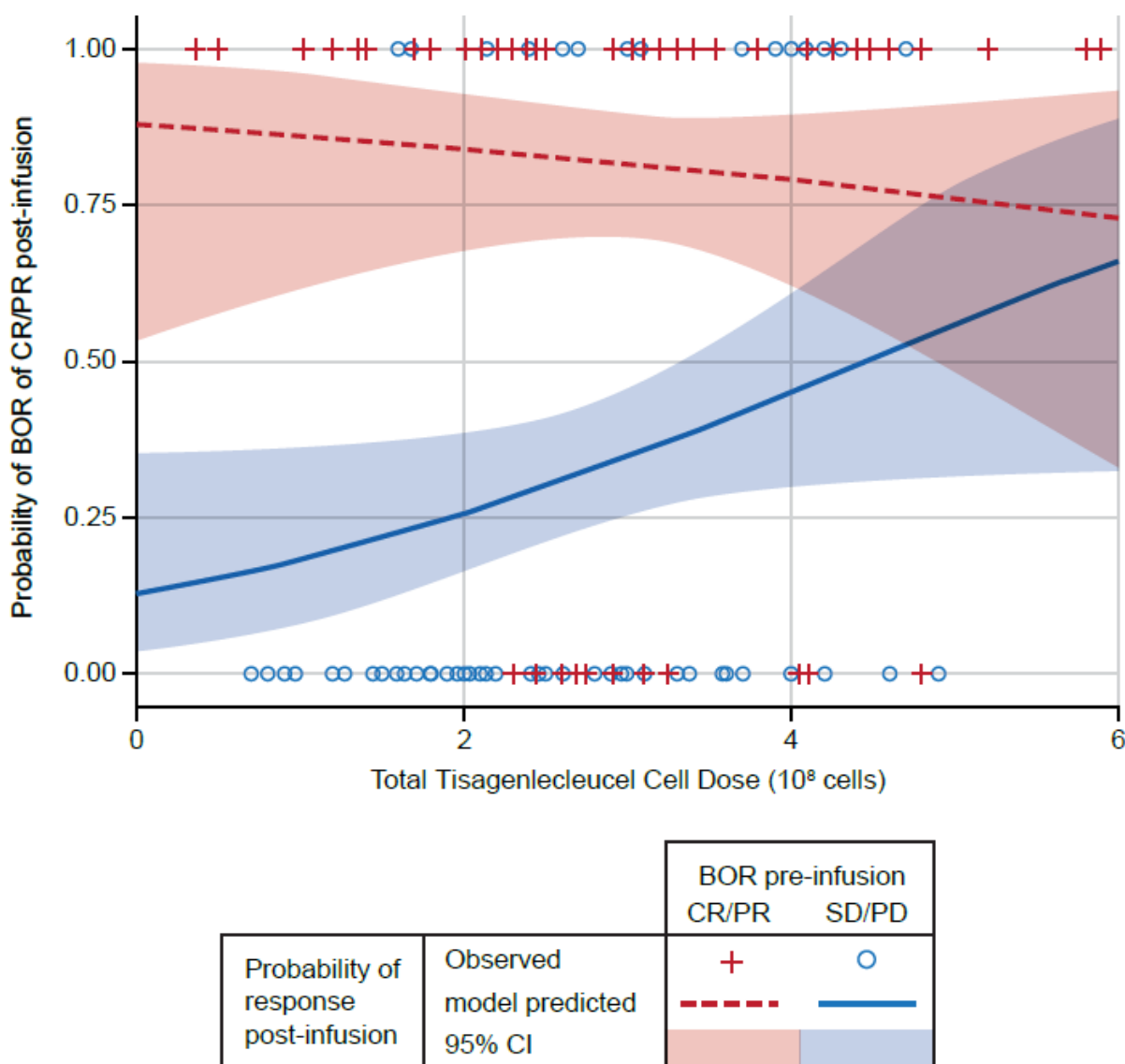
Figure S8. Probability of Response to Tisagenlecleucel Increases with Dose in Patients with PD/SD Pre-Infusion (blue). Patients with PR/CR Pre-Infusion (red) Have a Similar Probability of Response Across the Dose Range.

Figure shows predicted probabilities with 95% CI from logistic regression modeling analyses considering dose, status before infusion, and an interaction between the two.

BOR denotes best overall response, CI confidence interval, CR complete response, PD progressive disease, PR partial response, and SD stable disease.
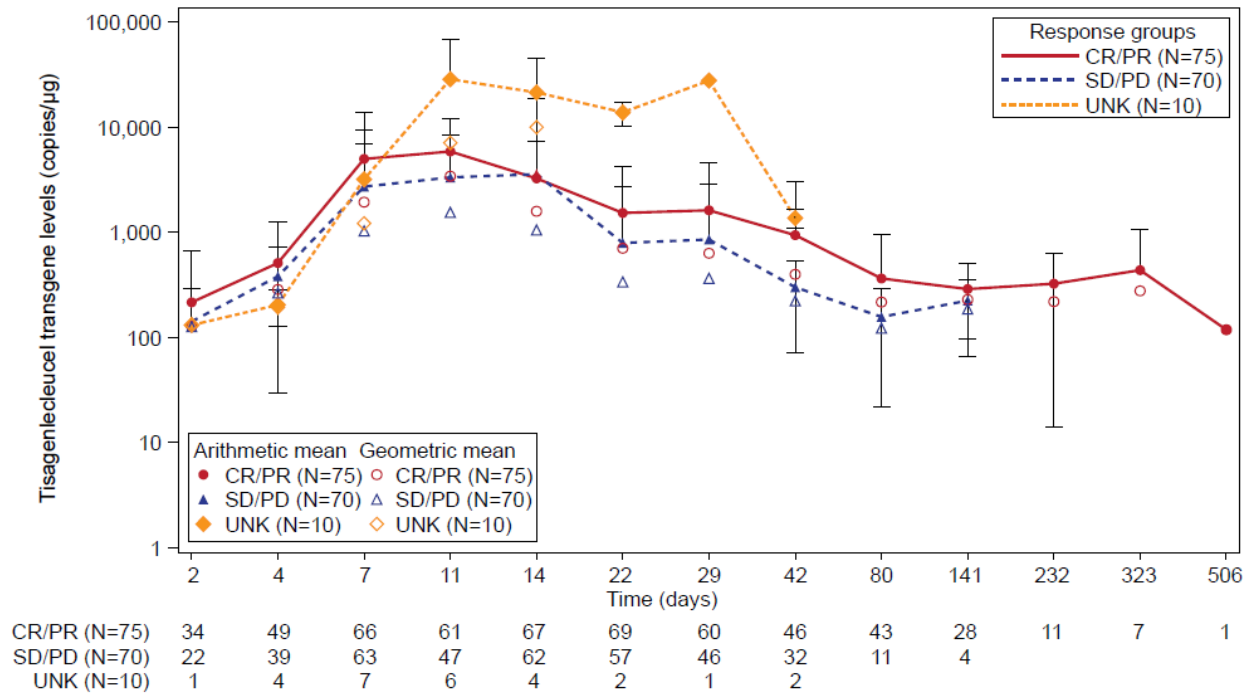
Figure S9. Geometric and Arithmetic Mean Concentration-Time Profiles for Tisagenlecleucel in Peripheral Blood by BOR Following Infusion for Patients in the Tisagenlecleucel Arm.

BOR denotes best overall response, CR complete response, PD progressive disease, PR partial response, SD stable disease, and UNK unknown.
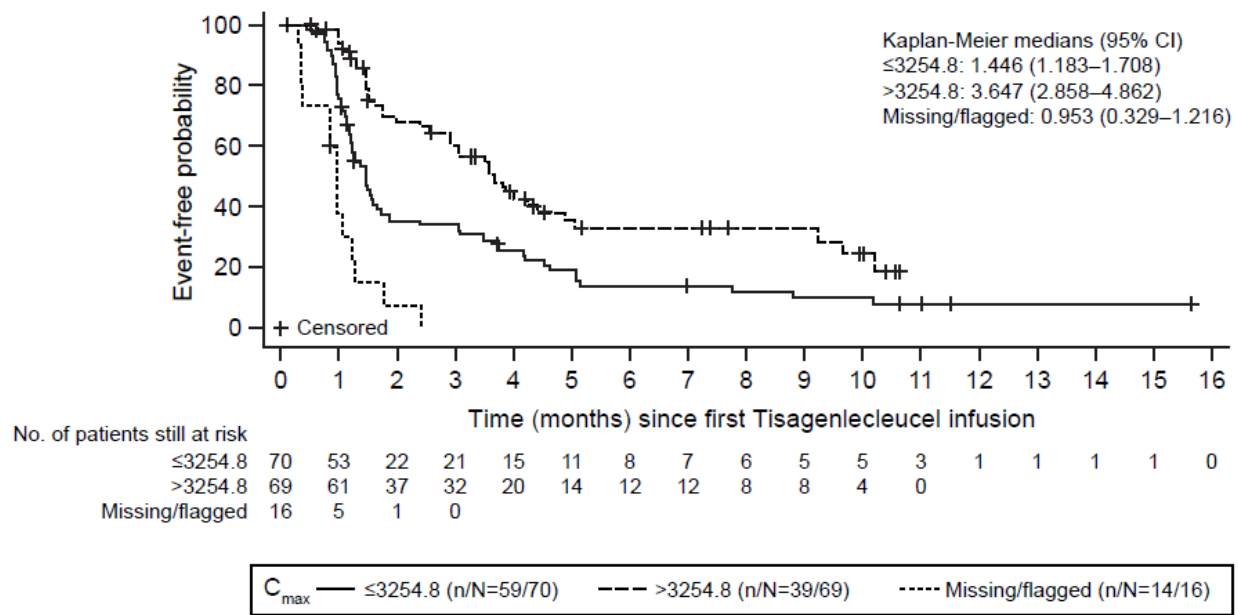
Figure S10. Kaplan-Meier Plot of EFS by Median Peak Expansion.

CI denotes confidence interval, C_{max} maximum serum concentration, and EFS event-free survival.

SUPPLEMENTARY TABLES

Table S1. Representativeness of Study Participants.

Category	Description
Disease, problem, or condition under investigation	Aggressive B-cell non-Hodgkin lymphomas
Special considerations related to	
Sex and gender	According to literature (cancer.org), the risk of non-Hodgkin lymphoma is higher in men than in women
Age	Older age is a greater risk factor for lymphoma overall
Race or ethnic group	White and non-Hispanic people are at highest risk of non-Hodgkin lymphoma, while Asian/Pacific Islander, American Indian, and Black populations are at the lowest risk
Geography	Throughout the world, non-Hodgkin lymphoma is more common in developed countries, with the US and Europe having higher prevalence
Other considerations	
Overall representativeness of this trial	The participants in the present trial demonstrated a prevalence of male (62.4) versus female (37.6) as in the general lymphoma population. Options on the case report form included male, female, unknown, or undifferentiated. Only adult patients (≥18 years of age) were eligible to participate in the trial and the age distribution in BELINDA is between 19 to 79 years of age; the majority of

	patients were <65 years old (68.9%) as it would be expected in a transplant eligible population required by the protocol. This trial enrolled patients internationally, with approximately 70% of patients belonging to the non-US countries and 30% of patients from the US region. The majority of the patients enrolled were White (79.5%), which is consistent with the overall risk factor data for the disease in the literature. The proportion of Asian patients who underwent randomization was 13%, while the proportion of Black patients was overall small (3.4%), but among patients enrolled in United States, slightly lower than the total population distribution of Black people in the US. Options on the case report form included White, Black or African American, Asian, and Native Hawaiian or Other Pacific Islander

Table S2. Number of Cycles/Regimens of Bridging/Salvage Chemotherapy Received as Part of Treatment Strategy.

	Tisagenlecleucel Arm			SOC Arm		
			All			All
	US	Non-US	Patients	US	Non-US	Patients
	(N=48)	(N=114)	(N=162)	(N=47)	(N=113)	(N=160)
No bridging/salvage	17 (35.4)	10 (8.8)	27 (16.7)	0	2 (1.8)	2 (1.3)
1 cycle of bridging/salvage	21 (43.8)	37 (32.5)	58 (35.8)	1 (2.1)	2 (1.8)	3 (1.9)
≥2 cycles/regimens of bridging/salvage	10 (20.8)	67 (58.8)	77 (47.5)	46 (97.9)	109 (96.5)	155 (96.9)

SOC denotes standard of care and US United States.

Table S3. Primary Disease History and Prior Antineoplastic Therapies in Arm A Patients by Number of Cycles of Bridging Therapy.

Demographic Variable	No Bridging (N=27)	1 Cycle of Bridging (N=58)	>1 Cycle/Regimen of Bridging (N=77)
Median age, years (range)	60.0 (25–79)	58.0 (21–76)	60.0 (19–75)
Age category ≥65 years – no. (%)	12 (44.4)	17 (29.3)	25 (32.5)
Sex, M – no. (%)	17 (63.0)	40 (69.0)	46 (59.7)
Region – no. (%)			
Non-US	10 (37.0)	37 (63.8)	67 (87.0)
US	17 (63.0)	21 (36.2)	10 (13.0)
ECOG performance status 1 – no. (%)	11 (40.7)	22 (37.9)	37 (48.1)
Diagnosis at disease – no. (%)			
DLBCL-NOS	17 (63.0)	35 (60.3)	49 (63.6)
HGBL with *MYC* and *BCL2* and/or *BCL6*	2 (7.4)	13 (22.4)	17 (22.1)
PMBCL	2 (7.4)	6 (10.3)	4 (5.2)
HGBL-NOS	0	3 (5.2)	4 (5.2)
FL grade 3B	3 (11.1)	0	2 (2.6)
T/HRBCL	2 (7.4)	1 (1.7)	0

Demographic Variable	No Bridging (N=27)	1 Cycle of Bridging (N=58)	>1 Cycle/Regimen of Bridging (N=77)
B-cell lymphoma, unclassifiable	0	0	1 (1.3)
Intravascular LBCL	1 (3.7)	0	0
Remission duration – no. (%)			
Refractory	19 (70.4)	33 (56.9)	55 (71.4)
Relapsed <6 months	7 (25.9)	11 (19.0)	12 (15.6)
Relapsed 6-12 months	1 (3.7)	14 (24.1)	10 (13.0)
IPI at study entry – no. (%)			
<2	15 (55.6)	24 (41.4)	17 (22.1)
≥2	12 (44.4)	34 (58.6)	60 (77.9)
Stage at time of study entry – no. (%)			
I	4 (14.8)	6 (10.3)	5 (6.5)
I E	0	1 (1.7)	3 (3.9)
II	6 (22.2)	12 (20.7)	9 (11.7)
II E	1 (3.7)	3 (5.2)	2 (2.6)
II Bulky	0	1 (1.7)	2 (2.6)
III	7 (25.9)	10 (17.2)	12 (15.6)
IV	9 (33.3)	25 (43.1)	44 (57.1)

DLBCL denotes diffuse large B-cell lymphoma, ECOG Eastern Cooperative Oncology Group,

FL follicular lymphoma, HGBL high-grade B-cell lymphoma, IPI International Prognostic Index,

LBCL large B-cell lymphoma, NOS not otherwise specified, PMBCL primary mediastinal B-cell

lymphoma, T/HRBCL T-cell/histiocyte-rich large B-cell lymphoma, and US United States.

Table S4. Time to Tisagenlecleucel Infusion.

	US (N=46)	Non-US (N=109)	All Patients (N=155)
Leukapheresis to infusion date (days)			
n	46	109	155
Mean (SD)	43.5 (11.69)	58.8 (14.52)	54.3 (15.38)
Median	41.0	57.0	52.0
Q1-Q3	36.0-45.0	50.0-63.0	43.0-61.0
Min-Max	31-91	38-135	31-135
Receipt of apheresis to shipment date (days)			
n	46	96	142
Mean (SD)	24.1 (2.55)	30.5 (11.27)	28.4 (9.83)
Median	23.5	28.0	26.0
Q1-Q3	23.0-24.0	25.0-33.0	24.0-31.0
Min-Max	22-34	22-115	22-115
Shipment date to infusion date (days)			
n	46	96	142
Mean (SD)	14.0 (10.30)	17.7 (11.73)	16.5 (11.39)
Median	11.0	15.0	14.0
Q1-Q3	9.0-15.0	11.0-21.5	10.0-20.0

	US	Non-US	All Patients
	(N=46)	**(N=109)**	**(N=155)**
Min-Max	4-63	2-91	2-91

SD denotes standard deviation and US United States.

Table S5. Adjusted Stratified Cox Models for Event-free Survival per BIRC and Overall Survival.

	Event-Free Survival	Overall Survival
	HR (95% CI)	HR (95% CI)
Tisagenlecleucel arm (vs SOC arm)	0.95 (0.72–1.25)	0.99 (0.64–1.52)
Age (per 10 years)	0.91 (0.80–1.04)	0.91 (0.74–1.13)
Male (vs female)	1.17 (0.85–, 1.60)	1.10 (0.69–, 1.75)
Race (vs White)		
Asian	1.20 (0.79–1.84)	1.18 (0.60–2.34)
Black	0.44 (0.17–1.11)	0.65 (0.19–2.16)
Other	0.73 (0.22–2.45)	1.37 (0.18–10.71)
Unknown	1.27 (0.56–2.88)	1.19 (0.35–4.01)
ECOG 1 (vs 0)	1.54 (1.14–2.10)	2.12 (1.33–3.36)
Histology (vs DLBCL-NOS)		
PMBCL	1.98 (0.67–5.82)	0.56 (0.07–4.44)
HGBL	3.85 (1.44–10.29)	4.99 (1.11–22.32)
FL3B	5.02 (1.30–19.32)	2.24 (0.28–17.72)
Other	2.28 (0.70–7.44)	4.74 (0.79–28.38)
DLBCL cell of origin (vs GCB)		
Non-GCB	0.80 (0.55–1.15)	0.64 (0.34–1.20)
Unknown	0.46 (0.17–1.20)	0.53 (0.34–1.20)
Stage III/IV (vs I/II)	1.51 (1.04–2.19)	1.68 (0.92–3.07)

Model stratified by randomization stratification factors: Region, remission duration, and IPI.

CIs are not adjusted for multiplicity, and no inference can be made on the statistical significance of the results.

BIRC denotes blinded independent review committee, CI confidence interval, DLBCL diffuse large B-cell lymphoma, ECOG Eastern Cooperative Oncology Group, FL3B follicular lymphoma grade 3B, GCB germinal center B cell, HGBL high-grade B-cell lymphoma, HR hazard ratio, IPI International Prognostic Index, NOS not otherwise specified, PMBCL primary mediastinal B-cell lymphoma, and SOC standard of care.

Table S6. Multivariate Cox Regression Model for Post-Infusion Modified Event-free Survival in Arm A.

Variable	Point Estimate	95% Wald Confidence Limits	
		HR Estimates	
ECOG status (0 vs 1)	0.73	0.47	1.14
Bridging cycles (1 vs 0)	1.10	0.58	2.11
Bridging cycles (≥2 vs 0)	1.43	0.78	2.64
Sex (female vs male)	0.60	0.38	0.94
HGBL vs non-HGBL	1.99	1.23	3.20
Refractory/relapsed <6 months vs relapsed 6-12 months	0.85	0.45	1.61
IPI (<2 vs ≥2)	0.86	0.53	1.39
Region (US vs Non-US)	0.86	0.54	1.35
Dose for patients with SD/PD before infusion (per 1×10^8 increase)	0.73	0.57	0.93
Dose for patients with CR/PR before infusion (per 1×10^8 increase)	1.26	0.91	1.73
SD/PD before infusion vs CR/PR before infusion at mean dose	2.30	1.44	3.66

A HR <1 means a decrease in the hazard of an event. CIs are not adjusted for multiplicity, and no inference can be made on the statistical significance of the results.

CI denotes confidence interval, CR complete response, ECOG Eastern Cooperative Oncology Group, HGBL high-grade B-cell lymphoma, HR hazard ratio, IPI International Prognostic Index, PD progressive disease, PR partial response, SD stable disease, and US United States.

Table S7. Multivariate Logistic Regression Model for Post-infusion Modified Best Overall Response (CR/PR vs SD/PD/UNK) in Arm A.

Variable	Odds Ratio Estimates		
	Point Estimate	95% Wald Confidence Limits	
ECOG status (1 vs 0)	0.39	0.17	0.89
Bridging cycles (1 vs 0)	0.85	0.25	2.82
Bridging cycles (≥2 vs 0)	1.00	0.29	3.48
Sex (male vs female)	0.48	0.20	1.14
non-HGBL vs HGBL	1.79	0.67	4.74
Relapsed 6-12 months vs refractory/relapsed <6 months	1.16	0.33	4.13
IPI (≥2 vs <2)	0.77	0.31	1.88
Region (US vs Non-US)	0.61	0.24	1.56
Dose for patients with SD/PD before infusion (per 1×10^8 increase)	1.61	0.98	2.63
Dose for patients with CR/PR before infusion (per 1×10^8 increase)	0.93	0.51	1.70
CR/PR before infusion vs SD/PD before infusion at mean dose	7.75	3.23	18.62

The odds ratio is the odds of having an modified best overall response of CR/PR vs SD/PD/UNK (i.e., an odds ratio >1 means patients are more likely to have a modified best

overall response of CR/PR). CIs are not adjusted for multiplicity, and no inference can be made on the statistical significance of the results.

CI denotes confidence interval, CR complete response, ECOG Eastern Cooperative Oncology Group, HGBL high-grade B-cell lymphoma, IPI International Prognostic Index, PD progressive disease, PR partial response, SD stable disease, UNK unknown, and US United States.

Table S8. Overall Safety Profile by Treatment Arm.*

	Tisagenlecleucel Arm N=162		SOC Arm N=160	
	All grades no. (%)	Grade ≥3 no. (%)	All grades no. (%)	Grade ≥3 no. (%)
AEs	160 (98.8)	136 (84.0)	158 (98.8)	144 (90.0)
Treatment-related[†]	152 (93.8)	121 (74.7)	151 (94.4)	137 (85.6)
SAEs	76 (46.9)	58 (35.8)	82 (51.3)	68 (42.5)
Treatment-related[†]	61 (37.7)	44 (27.2)	58 (36.3)	50 (31.3)
Fatal SAEs	11 (6.8)	11 (6.8)	5 (3.1)	5 (3.1)
Treatment-related[†]	4 (2.5)	4 (2.5)	1 (0.6)	1 (0.6)
AEs leading to dose adjustment/interruption[‡]	20 (12.3)	11 (6.8)	27 (16.9)	16 (10.0)
AEs requiring additional therapy	150 (92.6)	104 (64.2)	154 (96.3)	139 (86.9)

*During the safety comparison period, defined as from day of randomization to the earlier of:

- 56 days after last dose of study treatment

- Start date of new anticancer therapy

[†]Related to any part of the treatment strategy.

[‡]Dose adjustment/interruption for any treatment that is part of the treatment strategy.

AEs denotes adverse events, SAEs serious adverse events, and SOC standard of care.

Table S9. Cytokine Release Syndrome and Neurological Events Following Tisagenlecleucel Infusion.

	Tisagenlecleucel Arm N=155	Crossover from SOC Arm N=81
CRS – no. (%)		
Any grade	95 (61.3)	61 (75.3)
Grade ≥3	8 (5.2)	4 (4.9)
CRS management – no. (%)		
Tocilizumab	49 (51.6)	34 (55.7)
1 dose	28 (29.5)	18 (29.5)
≥2 doses	21 (13.5)	16 (19.8)
Corticosteroids	16 (16.8)	7 (11.5)
Other anticytokine therapy*	2 (1.3)	0
Median time to CRS onset, days (min–max)	4 (1–27)	3 (1–15)
Median time to CRS resolution, days (95% CI)	5 (4–5)	4 (4–5)
Serious NE – no. (%)		
Any grade	16 (10.3)	12 (14.8)
Grade ≥3	3 (1.9)	2 (2.5)
Median time to NE onset, days (min–max)	5 (3–93)	4.5 (2–24)
Median time to NE resolution, days (95% CI)	9 (3–14)	9 (2–n/e)

*To treat CRS that was refractory to tocilizumab; 1 received siltuximab, and the other received siltuximab, anakinra, and dasatinib.

CI denotes confidence interval, CRS cytokine release syndrome, NE neurological events, n/e

not estimable, and SOC standard of care.

Table S10. Most Common Adverse Events by Treatment Arm.*

AEs in >10% of Patients in Either Arm	Tisagenlecleucel Arm N=162		SOC Arm N=160	
	All grades no. (%)	Grade ≥3 no. (%)	All grades no. (%)	Grade ≥3 no. (%)
Number of patients with at least 1 event	160 (98.8)	136 (84.0)	158 (98.8)	144 (90.0)
Anemia	80 (49.4)	54 (33.3)	115 (71.9)	92 (57.5)
Nausea	67 (41.4)	2 (1.2)	79 (49.4)	10 (6.3)
Thrombocytopenia	59 (36.4)	52 (32.1)	79 (49.4)	76 (47.5)
Neutropenia	67 (41.4)	65 (40.1)	65 (40.6)	63 (39.4)
CRS	95 (58.6)	8 (4.9)	0	0
Hypokalemia	45 (27.8)	8 (4.9)	49 (30.6)	14 (8.8)
Diarrhea	35 (21.6)	3 (1.9)	58 (36.3)	6 (3.8)
Pyrexia	42 (25.9)	0	50 (31.3)	3 (1.9)
Constipation	48 (29.6)	0	42 (26.3)	0
Fatigue	38 (23.5)	3 (1.9)	49 (30.6)	6 (3.8)
Platelet count decrease	36 (22.2)	33 (20.4)	51 (31.9)	49 (30.6)
Neutrophil count decrease	41 (25.3)	41 (25.3)	30 (18.8)	30 (18.8)
Headache	37 (22.8)	0	32 (20.0)	1 (0.6)
Febrile neutropenia	21 (13.0)	21 (13.0)	40 (25.0)	40 (25.0)
Vomiting	24 (14.8)	1 (0.6)	35 (21.9)	3 (1.9)
Blood creatinine increase	29 (17.9)	2 (1.2)	29 (18.1)	1 (0.6)
Leukopenia	22 (13.6)	21 (13.0)	30 (18.8)	28 (17.5)

AEs in >10% of Patients in Either Arm	Tisagenlecleucel Arm N=162		SOC Arm N=160	
	All grades no. (%)	Grade ≥3 no. (%)	All grades no. (%)	Grade ≥3 no. (%)
Hypomagnesemia	20 (12.3)	0	29 (18.1)	2 (1.3)
Abdominal pain	17 (10.5)	2 (1.2)	30 (18.8)	5 (3.1)
WBC count decrease	19 (11.7)	18 (11.1)	22 (13.8)	19 (11.9)
Decreased appetite	21 (13.0)	1 (0.6)	17 (10.6)	1 (0.6)
Dyspnea	15 (9.3)	2 (1.2)	21 (13.1)	3 (1.9)
Edema peripheral	18 (11.1)	0	18 (11.3)	0
Dizziness	19 (11.7)	0	14 (8.8)	0
Cough	18 (11.1)	0	13 (8.1)	0
Hypophosphatemia	13 (8.0)	6 (3.7)	17 (10.6)	4 (2.5)
Asthenia	8 (4.9)	1 (0.6)	19 (11.9)	2 (1.3)
Mucosal inflammation	5 (3.1)	1 (0.6)	18 (11.3)	5 (3.1)

*During the safety comparison period, defined as from day of randomization to the earlier of:

- 56 days after last dose of study treatment

- Start date of new anticancer therapy

AEs denotes adverse events, CRS cytokine release syndrome, SOC standard of care, and WBC white blood cell.

Table S11. Causes of Death Following Randomization.

	Tisagenlecleucel Arm N=162	SOC Arm N=160
Deaths – no. (%)	52 (32.1)	45 (28.1)
Study indication (underlying disease)	42 (25.9)	32 (20.0)
Other	10 (6.2)	13 (8.1)
General disorders and administration site conditions – no. (%)	3 (1.9)	3 (1.9)
Death	2 (1.2)	1 (0.6)
Multiple organ dysfunction syndrome	0	2 (1.3)
Euthanasia	1 (0.6)	0
Hepatobiliary disorders	1 (0.6)	0
Hepatic failure	1 (0.6)	0
Infections and infestations	5 (3.1)	5 (3.1)
SARS-CoV-2 pneumonia	2 (1.2)	1 (0.6)
Septic shock	0	2 (1.3)
Bacterial sepsis	1 (0.6)	0
SARS-CoV-2	0	1 (0.6)
Enterococcal sepsis	1 (0.6)	0
Pseudomonal sepsis	1 (0.6)	0
Sepsis	0	1 (0.6)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	1 (0.6)	0

	Tisagenlecleucel Arm N=162	SOC Arm N=160
Sarcomatoid carcinoma of the lung	1 (0.6)	0
Psychiatric disorders	0	1 (0.6)
Completed suicide	0	1 (0.6)
Respiratory, thoracic, and mediastinal disorders	0	4 (2.5)
Acute respiratory failure	0	1 (0.6)
Pneumonitis	0	1 (0.6)
Pulmonary embolism	0	1 (0.6)
Respiratory failure	0	1 (0.6)

SARS-CoV-2 denotes coronavirus disease 2019 and SOC standard of care.