Supplementary Appendix

Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of phase 3 TRANSFORM study

Jeremy S. Abramson, Scott R. Solomon, Jon Arnason, et al.

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List of study sites

Study site	City	State/province/ prefecture	Country
Universitair Ziekenhuis Gent	Gent	Oost-Vlaanderen	Belgium
Centre Hospitalier Lyon Sud	Pierre-Bénite	Auvergne-Rhône-Alpes	France
CHRU de Lille, Hôpital Claude Huriez	Lille	Hauts-de-France	France
Gustave Roussy Cancer Center	Villejuif	Île-de-France	France
Institut Paoli-Calmettes	Marseille	Provence-Alpes-Côte d'Azur	France
Klinikum der Universität München	München	Bavaria	Germany
Helios Klinikum Berlin-Buch	Berlin	Berlin	Germany
Universitätsklinikum Hamburg-Eppendorf	Hamburg	Hamburg	Germany
Universitätsklinikum Carl Gustav Carus Dresden	Dresden	Sachsen	Germany
A. O. U. Citta della Salute e della Scienza di Torino	Torino	Torino	Italy
Istituto Clinico Humanitas	Rozzano	Milan	Italy
National Cancer Center Hospital	Tokyo	Tokyo	Japan
Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital	Tokyo	Tokyo	Japan
Toranomon Hospital	Tokyo	Tokyo	Japan
Osaka City University Hospital	Osaka-City	Osaka	Japan
Erasmus Medical Center	Rotterdam	—	Netherlands
Hospital Clínic i Provincial de Barcelona	Barcelona	Catalonia	Spain
Hospital Universitario 12 de Octubre	Madrid	Madrid	Spain

Study site	City	State/province/ prefecture	Country
Karolinska University Hospital	Stockholm	Södermanland and Uppland	Sweden
Medical Oncology, Inselspital, University Hospital Bern	Bern	Bern	Switzerland
University College London Hospitals	London	—	United Kingdom
Somers Cancer Research Building MP824 University Hospital	Southampton	—	United Kingdom
Mayo Clinic Hospital – Arizona	Phoenix	Arizona	United States
Virginia G. Piper Cancer Center – HonorHealth Research Institute	Scottsdale	Arizona	United States
UCSF Medical Center	San Francisco	California	United States
UCHealth University of Colorado Hospital	Aurora	Colorado	United States
Moffitt Cancer Center	Tampa	Florida	United States
Northside Hospital	Atlanta	Georgia	United States
Winship Cancer Institute – Emory Bone Marrow and Stem Cell Transplant Center	Atlanta	Georgia	United States
UPMC Hillman Cancer Center	Pittsburgh	Pennsylvania	United States
Beth Israel Deaconess Medical Center	Boston	Massachusetts	United States
Massachusetts General Hospital	Boston	Massachusetts	United States
John Theurer Cancer Center at Hackensack University Medical Center	Hackensack	New Jersey	United States
Barbara Ann Karmanos Cancer Institute	Detroit	Michigan	United States

Study site	City	State/province/ prefecture	Country
University of Michigan Health System	Ann Arbor	Michigan	United States
University of Minnesota	Minneapolis	Minnesota	United States
Mayo Clinic – Rochester	Rochester	Minnesota	United States
University of Nebraska Medical Center, Peggy D. Cowdery Patient Care Center	Omaha	Nebraska	United States
Northwestern University Feinberg School of Medicine	Chicago	Illinois	United States
Roswell Park Cancer Institute	Buffalo	New York	United States
Memorial Sloan Kettering Cancer Center	New York	New York	United States
University of Oklahoma Peggy and Charles Stephenson Cancer Center	Oklahoma City	Oklahoma	United States
Oregon Health & Science University	Portland	Oregon	United States
Baylor University Medical Center	Dallas	Texas	United States
The University of Texas MD Anderson Cancer Center	Houston	Texas	United States
Virginia Commonwealth University	Richmond	Virginia	United States
Fred Hutchinson Cancer Research Center	Seattle	Washington	United States

STATISTICAL ANALYSES

Hierarchical testing strategy

To control for multiplicity, a hierarchical testing strategy was used for the primary (event-free survival [EFS]) and key secondary (complete response [CR] rate, progression-free survival [PFS], and overall survival [OS]) end points to control for type I error rate. For the primary analysis, the primary efficacy end point of EFS was presented descriptively (ie, not included in the hierarchical testing strategy), as a statistically significant improvement was demonstrated in the lisocabtagene maraleucel (liso-cel) arm compared with the standard of care (SOC) arm at the interim analysis. At the time of the prespecified interim analysis, the null hypothesis on OS was not rejected. As described in the statistical analysis plan, all key secondary end points were to be retested at the primary analysis if the null hypothesis was not rejected for any one of them at the interim analysis. Therefore, hypothesis testing on CR rate, PFS, and OS was to be performed hierarchically for the primary analysis. The significance threshold to reject the null hypothesis for the key secondary end points was ≤0.021 at the primary analysis (per O'Brien-Fleming boundary alpha spending function).

The primary analysis was conducted when 115 EFS events were accrued, out of the 119 targeted by the protocol, corresponding to the 96.6% of the information fraction. The stopping boundaries for efficacy were then revised accordingly based on the actual number for EFS events available for analysis.

SUBGROUP ANALYSES

The following variables (collected at baseline, unless otherwise specified) were considered in subgroup analyses:

- Secondary age-adjusted International Prognostic Index status: 0 or 1 versus 2 or 3
- Prior response status: refractory versus relapse to last prior therapy. The status is refractory if a patient achieved progressive disease (PD), stable disease (SD), partial response, or CR with relapse within 3 months to last prior therapy; otherwise, the status is relapsed
- Age: <65, ≥65 to <75, and ≥75 years at the time of randomization
- Sex: male versus female
- Ethnicity: Hispanic or Latino versus not Hispanic or Latino

- Region: Europe, United States, and Japan
- Race: White versus other races
- Eastern Cooperative Oncology Group performance status at screening: 0 and 1
- Sum of the product of perpendicular diameters: >50 cm^2 or ≤50 cm^2
- Lactate dehydrogenase: <500 unit/L or ≥500 unit/L
- Prior chemotherapy response status: chemotherapy refractory versus chemotherapy sensitive to last therapy. The status is chemotherapy refractory if a patient achieved SD or PD to last chemotherapy-containing regimen; otherwise, the status is chemotherapy sensitive
- Central nervous system (CNS) disease status: known CNS disease versus no known CNS disease at the time of randomization
- Histological and molecular subtype:
    - Non-Hodgkin lymphoma (NHL) type: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma grade 3B, high grade B-cell lymphoma with DLBCL histology, primary mediastinal B-cell lymphoma, or T-cell/histiocyte-rich large B-cell lymphoma
    - DLBCL subtype: DLBCL not otherwise specified de novo or DLBCL from transformed indolent NHL
    - DLBCL subtype based on cell of origin: germinal center B cell (GCB) or activated B cell, or non-GCB
    - NHL subtype based on chromosomal translocation: double-hit or triple-hit lymphoma versus non–double-hit or triple-hit lymphoma
- Bridging therapy status: impact of bridging therapy treatment effect versus SOC will be evaluated in patients receiving bridging therapy

SUPPORTIVE OS ANALYSES

Two-stage accelerated failure time (AFT) model

The 2-stage AFT model aimed to address the challenge of crossover by estimating the counterfactual survival times that would have been observed in the absence of crossover. For the TRANSFORM study, this method was implemented in 2 steps. In step 1, the acceleration factor associated with crossover (ie, the amount by which liso-cel was expected to increase a crossover patient's survival time) was estimated using a Weibull AFT model, controlling for

baseline and secondary baseline patient information. Specifically, secondary baseline information for crossover was assessed at or soon after confirmation of an EFS event. Baseline covariates included in the model were as follows: age, secondary age-adjusted International Prognostic Index (0 and 1 vs 2 and 3), best response on first line of treatment (relapse vs refractory), NHL type, CNS involvement, Ann Arbor stage, bone marrow involvement, presence of B-symptoms, and prior chemotherapy response status (chemotherapy refractory vs chemotherapy sensitive). Secondary baseline covariates were as follows: Eastern Cooperative Oncology Group performance status, hematology (hemoglobin, leukocytes, platelets, absolute lymphocytes, and absolute neutrophils), coagulation (fibrinogen), chemistry (lactate dehydrogenase), and inflammatory markers (ferritin, C-reactive protein). Baseline and secondary baseline covariates were selected based on clinical review. In step 2, counterfactual survival times for crossover patients were derived by shrinking their observed survival times according to the acceleration factor calculated in step 1. Once the counterfactual survival times of the SOC patients were obtained, these were compared with the observed survival times of liso-cel using a Cox proportional hazards regression model to derive the hazard ratio. Kaplan-Meier product limit was used to provide summary information and 95% confidence intervals, and OS rates were computed using Greenwood's formula.

Rank-preserving structural failure time (RPSFT) model

Similar to the 2-stage AFT model, the RPSFT model derived counterfactual survival times for crossovers to be compared with the liso-cel arm. In the TRANSFORM study, counterfactual survival times were derived through the time spent "off" liso-cel, the time spent "on" liso-cel, and the acceleration factor associated with crossover (ie, the amount by which liso-cel was expected to increase a crossover patient's survival time). The acceleration factor was derived by a process called g-estimation and was used to shrink survival times for crossovers in order to derive their counterfactual estimates. These counterfactual survival times were then compared with observed survival times of liso-cel using a Cox proportional hazards regression model to derive the hazard ratio. Kaplan-Meier product limit was used to provide summary information and 95% confidence intervals, and OS rates were computed using Greenwood's formula.

Table 1. Study end points

End point type	End point	Description	Time frame
Primary			
	EFS	Time from randomization to death from any cause, PD, failure to achieve CR or PR by 9 weeks post randomization,* or start of new antineoplastic therapy due to efficacy concerns, whichever occurs first	Up to 3 years post randomization
Key secondary			
	CR rate	Percentage of patients achieving a CR	Up to 3 years post randomization
	PFS	Time from randomization to PD or death from any cause, whichever occurs first	Up to 3 years post randomization
	OS	Time from randomization to time of death due to any cause	Up to last patient last visit
Secondary			
	ORR	Percentage of patients achieving an objective response of PR or better	Up to 3 years post randomization
	DOR	Time from first response to disease progression, start of new antineoplastic therapy due to efficacy concerns or death from any cause	Up to 3 years post randomization
	PFS on next line of treatment (PFS-2)	Time from randomization to second objective disease progression or death from any cause, whichever occurs first	Up to 3 years post randomization

	EFS rate	Percentage of patients free of any EFS event at fixed time points	At 6, 12, 24, and 36 months post randomization
	PFS rate	Percentage of patients free of any PFS event at fixed time points	At 6, 12, 24, and 36 months post randomization
	OS rate	Percentage of patients alive at fixed time points	At 6, 12, 24, and 36 months post randomization
	Clinical, histological, and molecular subgroup analyses	Response rate, EFS, PFS, OS in clinical, histological, and molecular subgroups	Up to 3 years post randomization
	Rate of HDCT completion	Percentage of patients in SOC arm completing HDCT	Up to 3 years post randomization
	Rate of HSCT completion	Percentage of patients in SOC arm completing autologous HSCT	Up to 3 years post randomization
	Response rate post-HSCT	Percentage of patients in response after undergoing autologous HSCT	At 3 months after autologous HSCT
	HRQOL (domains of interest)	HRQOL using the global health/QOL, fatigue, physical and cognitive functioning subscales of the European Organisation for Research and Treatment of Cancer–Quality of Life C30 Questionnaire, and the Functional Assessment of Cancer Therapy-Lymphoma “Additional concerns” Subscale	Up to 3 years post randomization

	Hospital resource utilization	Frequency of hospitalizations, inpatient days, intensive care unit days, outpatient visits, and reasons for hospitalization	Up to 3 years post randomization
	Safety	Type, frequency, and severity of adverse events, serious adverse events, and laboratory abnormalities (overall and in clinical, histological, and molecular subgroups)	Up to 3 years post randomization
Exploratory			
	Efficacy analyses for patients who crossed over to liso-cel	PFS, EFS, DOR, ORR, and CR rate for patients who crossed over to liso-cel	Up to 1 year after liso-cel infusion
	Efficacy analyses for patients who crossed over to liso-cel	OS for patients who crossed over to liso-cel	Up to last patient, last visit
	Cellular kinetics	Maximum expansion, time to maximum expansion, area under the curve, and other relevant cellular kinetic parameters of liso-cel as assessed by droplet digital polymerase chain reaction	Up to 3 years post randomization

CR, complete response; DOR, duration of response; EFS, event-free survival; HDCT, high-dose chemotherapy; HRQOL, health-related quality of life; HSCT, hematopoietic stem cell transplantation; IRC, independent review committee; liso-cel, lisocabtagene maraleucel; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SOC, standard of care.

*Failure to achieve CR or PR was evaluated after 3 cycles of platinum-based immunochemotherapy for the SOC arm (expected 9 weeks post randomization) and 5 weeks after the infusion for the liso-cel arm.

Table 2. Definition of analysis sets

Analysis set	Definition
Screened set	All patients who underwent screening
ITT set	All patients randomized to a treatment arm. This set was utilized in efficacy analyses
Safety set	All randomized patients who received at least one dose of study treatment.* This set was utilized in safety analyses
Cellular kinetic set	All patients who received liso-cel who had both preinfusion and at least 1 postinfusion cellular kinetic measurement assessed by droplet digital polymerase chain reaction
Crossover ITT set	All patients in the SOC arm who were approved for crossover to receive liso-cel
Crossover efficacy set	All patients in the SOC arm who were approved for crossover and received liso-cel infusion
Crossover safety set	All patients in the SOC arm who were approved for crossover and received CAR T-cell therapy (liso-cel or nonconforming product)

CAR, chimeric antigen receptor; ITT, intention-to-treat; liso-cel, lisocabtagene maraleucel; SOC, standard of care.

*In the liso-cel arm, study treatment included bridging therapy if needed, lymphodepleting chemotherapy, and liso-cel or nonconforming product (defined as any product wherein one of the CD8 or CD4 cell components did not meet one of the requirements to be considered liso-cel but was considered safe for infusion). In the SOC arm, study treatment included 3 cycles of platinum-based immunochemotherapy followed by high-dose chemotherapy and autologous stem cell transplantation in responding patients.

Table 3. Supportive OS analyses (ITT set)

	Liso-cel (n = 92)	SOC (n = 92)
Two-stage accelerated failure time model		
Patients with events, n (%)	28 (30)	38 (41)
Median (95% CI) time to event, mo	NR (29.5–NR)	NR (8.1–NR)
Stratified HR (95% CI)*	0.415 (0.251–0.686)	
12-month OS rate, %	83.4	54.1
Two-sided 95% CI†	75.7–91.1	43.1–65.2
18-month OS rate, %	73.1	54.1
Two-sided 95% CI†	63.9–82.3	43.1–65.2
Rank-preserving structural failure time model		
Patients with events, n (%)	28 (30)	31 (34)
Median (95% CI) time to event, mo	NR (29.5–NR)	11.4 (9.7–NR)
Stratified HR (95% CI)*	0.279 (0.145–0.537)	
12-month OS rate, %	83.4	49.7
Two-sided 95% CI†	75.7–91.1	30.7–68.8
18-month OS rate, %	73.1	NR
Two-sided 95% CI†	63.9–82.3	NR–NR

CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; liso-cel, lisocabtagene maraleucel; NR, not reached; OS, overall survival; SOC, standard of care.

*Based on a stratified Cox proportional hazards model.

†Greenwood's formula.

Table 4. Efficacy outcomes based on IRC assessment for patients by receipt of bridging therapy

	Liso-cel				
	PET-positive disease after bridging therapy (n = 47)*	**PET-negative disease after bridging therapy (n = 9)†**	**No bridging therapy (n = 34)**	**Total (n = 92)**	**SOC (n = 92)**
Best overall response, n (%)					
Complete response	34 (72)	8 (89)	25 (74)	68 (74)	40 (43)
Partial response	7 (15)	0	5 (15)	12 (13)	5 (5)
Stable disease	3 (6)	0	1 (3)	4 (4)	20 (22)
Progressive disease	2 (4)	1 (11)	2 (6)	6 (7)	24 (26)
Nonevaluable	1 (2)	0	1 (3)	2 (2)	3 (3)
EFS					
Median (95% CI) EFS, mo‡	NR (6.0–NR)	NR (2.2–NR)	12.2 (5.9–NR)	NR (9.5–NR)	2.4 (2.2–4.9)
12-month EFS rate, % (95% CI)§	56.5 (42.2–70.8)	77.8 (50.6–100.0)	52.9 (36.2–69.7)	57.1 (47.0–67.3)	22.5 (13.9–31.2)
18-month EFS rate, % (95% CI)§	54.3 (39.8–68.7)	66.7 (35.9–97.5)	46.7 (29.8–63.6)	52.6 (42.3–62.9)	20.8 (12.2–29.5)
PFS					
Median (95% CI) PFS, mo‡	NR (8.4–NR)	NR (2.2–NR)	NR (11.0–NR)	NR (12.6–NR)	6.2 (4.3–8.6)
12-month PFS rate, % (95% CI)§	60.9 (46.3–75.4)	77.8 (50.6–100.0)	62.5 (45.7–79.4)	63.1 (53.0–73.3)	31.2 (20.2–42.3)
18-month PFS rate, % (95% CI)§	58.4 (43.7–73.2)	66.7 (35.9–97.5)	55.6 (38.1–73.1)	58.2 (47.7–68.7)	28.8 (17.7–40.0)
OS					
Median (95% CI) OS, mo‡	NR (22.2–NR)	29.5 (5.9–NR)	NR (21.1–NR)	NR (29.5–NR)	29.9 (17.9–NR)
12-month OS rate, % (95% CI)§	82.4 (71.3–93.5)	88.9 (68.4–100.0)	85.3 (73.4–97.2)	83.4 (75.7–91.1)	72.0 (62.7–81.3)
18-month OS rate, % (95% CI)§	73.2 (60.1–86.2)	77.8 (50.6–100.0)	73.5 (58.7–88.4)	73.1 (63.9–82.3)	60.6 (50.2–71.1)

Two patients who received bridging therapy did not have the prelymphodepleting chemotherapy assessment.

CI, confidence interval; EFS, event-free survival; liso-cel, lisocabtagene maraleucel; IRC, independent review committee; NR, not reached; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival.

*Includes patients with PET-positive disease at prelymphodepleting chemotherapy assessment after receiving bridging therapy.

†Includes patients with PET-negative disease at prelymphodepleting chemotherapy assessment after receiving bridging therapy.

‡Median estimates of time to event were Kaplan-Meier product-limit estimates.

§Based on Greenwood's formula.

Table 5. Timing of crossover to receive liso-cel among patients in the SOC arm (ITT set)

Parameter	SOC (n = 92)
Patients approved for crossover to receive liso-cel, n (%)	61 (66)
Patients by timing of crossover approval*	
Before completion of SOC cycle 1	0
After completion of SOC cycle 1 and before completion of SOC cycle 2	5 (8)
After completion of SOC cycle 2 and before completion of SOC cycle 3	13 (21)
After completion of SOC cycle 3 and before HDCT/ASCT	22 (36)
After HDCT/ASCT	21 (34)

ASCT, autologous stem cell transplantation; HDCT, high-dose chemotherapy; ITT, intention-to-treat; liso-cel, lisocabtagene maraleucel; SOC, standard of care.

*Percentages are based on the number of patients approved for crossover to liso-cel treatment.

Table 6. Demographics and disease characteristics of patients at time of crossover (crossover ITT set)

Characteristic	Crossover subgroup (n = 61)
Male sex, n (%)	41 (67)
Age, y, n (%)	
Median (range)	60.0 (29–75)
<65	43 (70)
≥65 to <75	16 (26)
75	2 (3)
Large B-cell lymphoma subtypes, n (%)	
Diffuse LBCL NOS	33 (54)
Diffuse LBCL transformed from indolent lymphomas	6 (10)
FL grade 3B	0
HGBCL with gene rearrangements in *MYC* and *BCL2*, *BCL6*, or both*	15 (25)
Double-hit rearrangements	10 (16)
Triple-hit rearrangements	4 (7)
PMBCL	6 (10)
THRBCL	1 (2)
ECOG PS at time of crossover, n (%)	
0	25 (41)
1	35 (57)
2	1 (2)
Median (range) CrCl at time of crossover, mL/min	99.6 (43.8–246.6)
Median (range) LVEF at time of crossover, %	60 (39–71)
Secondary CNS lymphoma, n (%)	3 (5)
Best response to first-line therapy, n (%)	
CR	19 (31)
PR	30 (49)
SD	2 (3)
PD	10 (16)
Not evaluable	0

CNS, central nervous system; CR, complete response; CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma; ITT, intention-to-treat; LBCL, large B-cell lymphoma; liso-cel, lisocabtagene maraleucel; LVEF, left ventricular ejection fraction; NOS, not otherwise specified; PD, progressive disease; PMBCL, primary mediastinal B-cell lymphoma; PR, partial response; SD, stable disease; THRBCL, T-cell/histiocyte-rich large B-cell lymphoma.
*FISH results were assessed locally but subsequently confirmed by a central lab.

Table 7. Efficacy outcomes for patients in the crossover subgroup per investigator assessment (crossover efficacy set)

Efficacy end point	Crossover subgroup (n = 57)*
Median (range) follow-up, mo†	12.0 (1.4–28.1)
EFS	
Patients with events, n (%)	33 (58)
Median (95% CI) EFS, mo‡	5.9 (3.1–15.1)
12-month EFS rate, % (95% CI)§	45.2 (31.6–58.8)
Overall response rate, n (%)	35 (61)
Two-sided 95% CI	47.6–74.0
Complete response rate, n (%)	30 (53)
Two-sided 95% CI	39.0–66.0
Best overall response, n (%)	
Complete response	30 (53)
Partial response	5 (9)
Stable disease	1 (2)
Progressive disease	18 (32)
Nonevaluable	3 (5)
PFS	
Patients with events, n (%)	31 (54)
Median (95% CI) PFS, mo‡	5.9 (3.2–26.5)
12-month PFS rate, % (95% CI)§	46.9 (33.0–60.7)
OS	
Patients with events, n (%)	28 (49)
Median (95% CI) time to event, mo	15.8 (11.8–NR)
12-month OS rate, % (95% CI)§	63.1 (50.1–76.0)
Duration of response	
Patients with events, n (%)	11 (19)
Median (95% CI) DOR, mo‡	13.7 (9.4–23.5)
Duration of CR	
Patients with events, n (%)	8 (14)
Median (95% CI) DOR, mo‡	13.7 (13.7–20.5)

All end points were evaluated from the time of liso-cel infusion.

CAR, chimeric antigen receptor; CI, confidence interval; DOR, duration of response; EFS, event-free survival; IRC, independent review committee; liso-cel, lisocabtagene maraleucel; OS, overall survival; PFS, progression-free survival; SOC, standard of care.

*Three patients approved for crossover did not receive liso-cel and 1 patient received nonconforming product and were not included in the efficacy analyses.

†Includes all patients randomized to the SOC arm who were approved for crossover and received CAR T-cell therapy (n = 57).

‡Median estimates of time to event were Kaplan-Meier product-limit estimates.

§Based on Greenwood's formula.

Table 8. Grade 3–4 TEAEs (safety set)

TEAE	Liso-cel (n = 92)	SOC (n = 91)
Patients with ≥1 grade 3–4 TEAE	85 (92)	81 (89)
Grade 3–4 TEAEs occurring in ≥2% of patients		
Neutropenia	75 (82)	47 (52)
Anemia	48 (52)	51 (56)
Thrombocytopenia	46 (50)	62 (68)
Lymphopenia	24 (26)	9 (10)
Leukopenia	15 (16)	11 (12)
Febrile neutropenia	11 (12)	21 (23)
Platelet count decreased	7 (8)	2 (2)
Neutrophil count decreased	6 (7)	0
Hypertension	5 (5)	1 (1)
Headache	4 (4)	1 (1)
Hypokalemia	4 (4)	4 (4)
Hyponatremia	3 (3)	2 (2)
Hypophosphatemia	3 (3)	8 (9)
Hypotension	3 (3)	0
Muscular weakness	3 (3)	0
Nausea	3 (3)	4 (4)
White blood cell count decreased	3 (3)	0
Abdominal pain	2 (2)	1 (1)
Aphasia	2 (2)	0
Bone marrow failure	2 (2)	0
CD4 lymphocytes decreased	2 (2)	1 (1)
Constipation	2 (2)	0
Hyperglycemia	2 (2)	0
Infusion-related reaction	2 (2)	0
Pulmonary embolism	2 (2)	1 (1)
Sepsis	2 (2)	3 (3)
Syncope	2 (2)	1 (1)
Acute kidney injury	1 (1)	4 (4)
Alanine aminotransferase increased	1 (1)	2 (2)

TEAE	Liso-cel (n = 92)	SOC (n = 91)
Back pain	1 (1)	2 (2)
Confusional state	1 (1)	2 (2)
Decreased appetite	1 (1)	4 (4)
Deep vein thrombosis	1 (1)	2 (2)
Lymphocyte count decreased	1 (1)	2 (2)
Pain in extremity	1 (1)	2 (2)
Pneumonia	1 (1)	2 (2)
Urinary tract infection	1 (1)	2 (2)
Vomiting	1 (1)	2 (2)
Diarrhea	0	3 (3)
Electrolyte imbalance	0	2 (2)
Fatigue	0	2 (2)
Hyperuricemia	0	2 (2)
Mucosal inflammation	0	4 (4)
Pain	0	2 (2)
Stomatitis	0	2 (2)

A patient was counted only once for multiple events within a preferred term.

Liso-cel, lisocabtagene maraleucel; SOC, standard of care; TEAE, treatment-emergent adverse event.

Table 9. Summary of all deaths (safety set)

	Liso-cel (n = 92)	SOC (n = 91)	Crossover subgroup (n = 58)*	SOC + crossover subgroup (n = 91)
Deaths, n (%)	28 (30)	9 (10)	29 (50)	38 (42)
Disease progression	17 (18)	4 (4)	21 (36)	25 (27)
Adverse event	4 (4)	5 (5)	0	5 (5)
Other	7 (8)	0	5 (9)	5 (5)
Unknown cause of death	0	0	3 (5)	3 (3)

Liso-cel, lisocabtagene maraleucel; SOC, standard of care.

*Includes deaths that occurred after approval to receive liso-cel in patients randomized to the SOC arm who crossed over to receive liso-cel.

Table 10. TEAEs after CAR$^+$ T-cell infusion occurring in ≥10% of patients in the crossover subgroup (crossover safety set)

	Crossover subgroup (n = 58)*
Patients with ≥1 TEAE, n (%)	54 (93)
Neutropenia	31 (53)
Cytokine release syndrome	27 (47)
Anemia	24 (41)
Thrombocytopenia	21 (36)
Headache	16 (28)
Nausea	14 (24)
Fatigue	12 (21)
Constipation	11 (19)
Hypotension	11 (19)
Dizziness	10 (17)
Hypokalemia	10 (17)
Tremor	10 (17)
Diarrhea	9 (16)
Lymphopenia	9 (16)
Decreased appetite	8 (14)
Confusional state	7 (12)
Peripheral edema	7 (12)
Hypocalcemia	6 (10)
Pyrexia	6 (10)
Vomiting	6 (10)

CAR, chimeric antigen receptor; liso-cel, lisocabtagene maraleucel; TEAE, treatment-emergent adverse event.

*Of 61 patients approved for crossover, 3 did not receive CAR$^+$ T-cell infusion; the crossover safety set includes 57 patients who received liso-cel infusion and 1 who received nonconforming product.

Table 11. CRS and NE in patients in the crossover subgroup (crossover safety set)

	Crossover subgroup (n = 58)*
Patients with CRS,† n (%)	
Any grade	27 (47)
Grade 1	19 (33)
Grade 2	7 (12)
Grade 3	0
Grade 4	1 (2)
Grade 5	0
Median (range) time to onset, d	3.0 (1–8)
Median (range) time to resolution, d	6.0 (1–14)
Patients with NEs‡ n (%)	
Any grade	11 (19)
Grade 1	4 (7)
Grade 2	5 (9)
Grade 3	1 (2)
Grade 4	1 (2)
Grade 5	0
Median (range) time to onset, d	8.0 (2–21)
Median (range) time to resolution, d	11.0 (2–48)
Clinical management of CRS and/or NEs, n (%)	
Tocilizumab, corticosteroids, or both	
Tocilizumab and/or corticosteroids	22 (38)
Tocilizumab only	9 (16)
Tocilizumab and corticosteroids	10 (17)
Corticosteroids only	3 (5)
Vasopressors	1 (2)

CAR, chimeric antigen receptor; CRS, cytokine release syndrome; liso-cel, lisocabtagene maraleucel; NE, neurological event.

*Of 61 patients approved for crossover, 3 did not receive CAR^+ T-cell infusion; the crossover safety set includes 57 patients who received liso-cel infusion and 1 who received nonconforming product.

†Graded according to the Lee 2014 criteria.[1]

‡Defined as investigator-identified neurological adverse events related to liso-cel and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Table 12. Liso-cel cellular kinetic parameters by ddPCR in the liso-cel arm and crossover subgroup (cellular kinetic set)

Parameter	Liso-cel (n = 87)	Crossover subgroup (n = 56)
C_{max}, copies/µg		
Number of patients	84	52
Median	33,285	33,258
IQR	13,848–94,913	10,690–73,053
Range	549–475,991	143–454,083.5
t_{max}, day		
Number of patients	84	52
Median	10	10
IQR	9–11	8.5–14
Range	6–22	6–28
$AUC_{0–28d}$, day*copies/µg		
Number of patients	84	52
Median	268,911	305,970
IQR	114,626–779,701	124,621–804,128
Range	5158–4,836,898.5	2255–5,999,122

$AUC_{0–28d}$, area under the curve from 0 to 28 days postinfusion; C_{max}, maximum expansion; ddPCR, droplet digital polymerase chain reaction; IQR, interquartile range; liso-cel, lisocabtagene maraleucel; t_{max}, time to maximum expansion.

Noncompartmental cellular kinetic parameters were calculated for patients who had a quantifiable cellular kinetic measurement ≥28 days after infusion. Noncompartmental parameters were not calculated in the following cases: 1) if there were less than 2 quantifiable cellular kinetic measurements up to 28 days after infusion; or 2) if all cellular kinetic measurements were below the limit of detection.

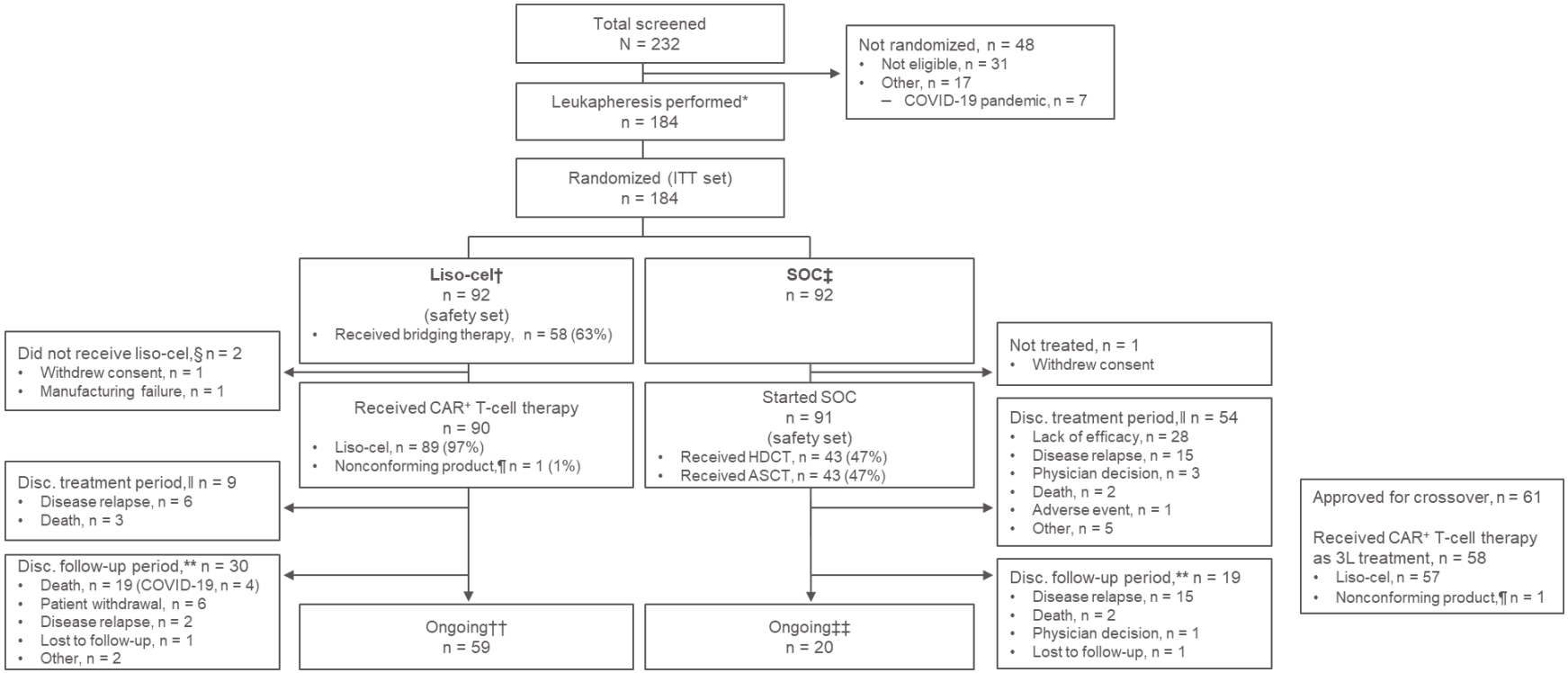
Table 13. Persistence of the liso-cel transgene in the liso-cel arm (cellular kinetic set)

Patients at time point*	Liso-cel
35 days postinfusion	61/67 (91%)
42 days postinfusion	53/62 (85%)
2 months postinfusion	47/68 (69%)
3 months postinfusion	41/70 (59%)
5 months postinfusion	30/61 (49%)
8 months postinfusion	22/49 (45%)
11 months postinfusion	19/44 (43%)
17 months postinfusion	11/34 (32%)
23 months postinfusion	5/15 (33%)

Liso-cel, lisocabtagene maraleucel.

*Number of patients with persistence of liso-cel in the blood/number of patients with an available sample at the specific time point. Percentage is 100 times n divided by N. Persistence was defined as a transgene count greater than or equal to the lower limit of detection (40 copies/μg). Data obtained after the start of a new anticancer therapy were not included in the determination of persistence.

Figure 1. Trial profile



3L, third line; ASCT, autologous stem cell transplantation; CAR, chimeric antigen receptor; disc., discontinued; HDCT, high-dose chemotherapy; ITT, intention-to-treat; LDC, lymphodepleting chemotherapy; SOC, standard of care.

*During screening, patients were assessed for eligibility, underwent unstimulated leukapheresis, and subsequent randomization.

†Patients received LDC followed by liso-cel infusion; bridging therapy was allowed per protocol.

‡Patients received 3 cycles of SOC platinum-based immunochemotherapy (see Methods for details) followed by HDCT and ASCT.

§Patients received bridging therapies and, therefore, were included in the safety set.

¶Nonconforming product was defined as any product wherein one of the CD8 or CD4 cell components did not meet one of the requirements to be considered liso-cel but was considered safe for infusion.

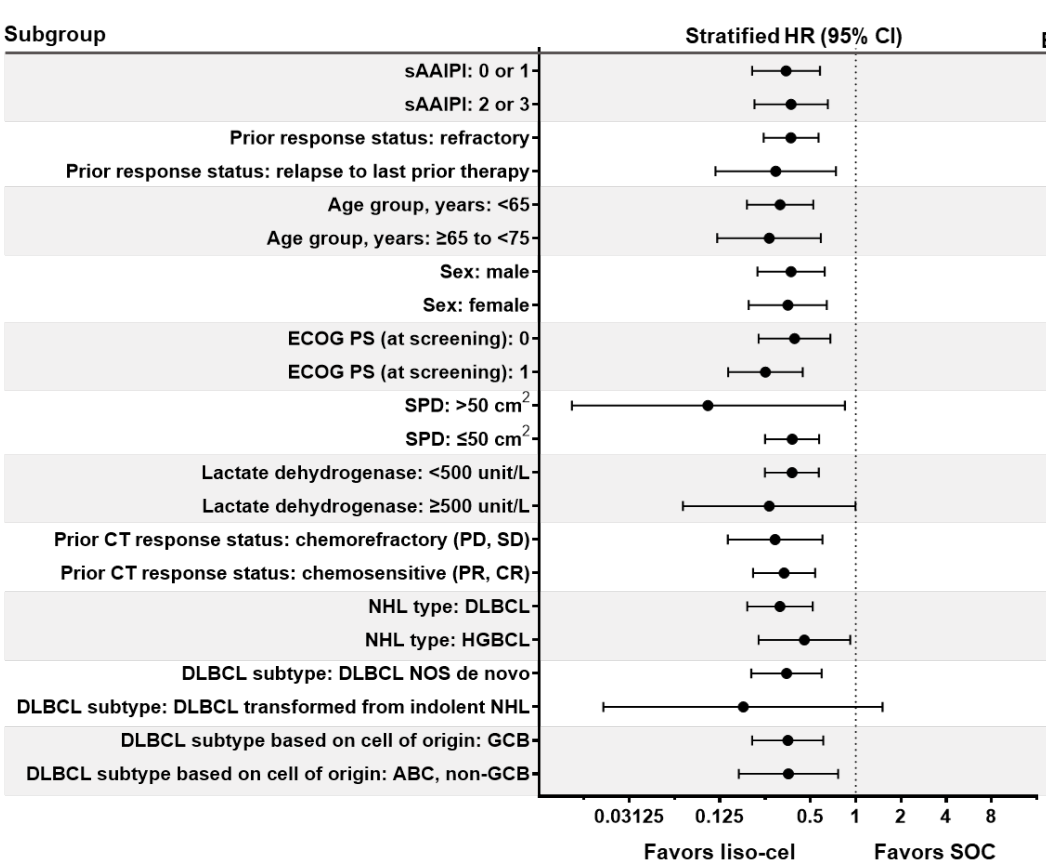
‖Patients could discontinue the treatment period, defined as the period from randomization to week 18, but continue to be followed up for OS.

**Patients could discontinue the follow-up period, defined as the period from week 18 to month 36, but continue to be followed up for OS.

††Six patients who discontinued the treatment period remained in the study follow-up period.

‡‡One patient who discontinued the treatment period remained in the study follow-up period.

Figure 2. Selected subgroup analysis of event-free survival per IRC (ITT set)



Kaplan-Meier estimates of event-free survival (primary end point) per IRC. Event-free survival was defined as the time from randomization to death from any cause, PD, not achieving a CR or PR by 9 weeks post randomization, or start of a new antineoplastic therapy due to efficacy concerns, whichever occurred first.

ABC, activated B cell; CI, confidence interval; CNS, central nervous system; CR, complete response; CT, chemotherapy; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B cell; HGBCL, high-grade B-cell lymphoma; HR, hazard ratio; IRC, independent review committee; ITT, intention-to-treat; liso-cel, lisocabtagene maraleucel; NHL, non-Hodgkin lymphoma; NOS, not otherwise specified; PD, progressive disease; PR, partial response; sAAIPI, secondary age-adjusted International Prognostic Index; SD, stable disease; SOC, standard of care; SPD, sum of the product of perpendicular diameters.

REFERENCE

1. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124(2):188-195.