Supplementary Appendix

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

Supplement to: 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;377:2531-44. DOI: 10.1056/NEJMoa1707447

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Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma

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Supplementary Appendix

Contents **Page**

List of Participating Sites

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- H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA
- Washington University, St. Louis, MO, USA
- Dana-Farber Cancer Institute, Boston, MA, USA
- Stanford University, Stanford, CA, USA
- University of Miami, Miami, FL, USA
- Montefiore Medical Center, Bronx, NY, USA
- Vanderbilt University Medical Center, Nashville, TN, USA
- City of Hope National Medical Center, Duarte, CA, USA
- Loyola University Medical Center, Maywood, IL, USA
- Mayo Clinic, Rochester, MN, USA
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- University of Rochester School of Medicine, Rochester, NY, USA
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- Cleveland Clinic, Cleveland, OH, USA
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- John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ, USA
- Banner MD Anderson Cancer Center, Gilbert, AZ, USA
- University of California at San Diego, San Diego, CA, USA
- Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel

Supplementary Methods

Patients and study design

Key eligibility criteria

Eligible patients had an absolute neutrophil count greater than 1,000 cells per microliter, an absolute lymphocyte count greater than 100 cells per microliter, a platelet count greater than 75,000 cells per microliter, adequate organ function, no central nervous system involvement, and no active infection. Adequate organ function refers to renal, hepatic, pulmonary, and cardiac eligibility requirements and were defined as the following:

- Creatinine clearance (as estimated by Cockcroft Gault) ≥ 60 mL/min
- Serum ALT/AST ≤ 2.5 ULN
- Total bilirubin ≤1.5 mg/dl, except in subjects with Gilbert's syndrome.
- Cardiac ejection fraction ≥ 50% with no evidence of pericardial effusion as determined by an ECHO, and no clinically significant ECG findings
- No clinically significant pleural effusion
- Baseline oxygen saturation >92% on room air

CAR T-cell dosing

Patients weighing less than 100 kg received a target dose of 2×10^6 CAR T cells/kg. If a patient weighed ≥ 100kg, they received a fixed dose of 2×10^8 CAR T cells. The minimum dose was of 1×10^6 CAR T cells per kilogram.

CD19 immunohistochemistry

A screening assay for determination of CD19 positivity was not employed, and baseline CD19 status was determined centrally by a validated immunohistochemistry method (NeoGenomics) and retrospectively evaluated by a trained pathologist as a part of central review. Expression level by immunohistochemical staining intensity (clone LE CD19 [Dako]) was graded as either 1,

2, or 3 and multiplied by the percent of cells that are positive for each level as shown in the formula below[1]:

CD19 H-Score = [1 × (% cells 1+) + 2 × (% cells 2+) + 3 × (% cells 3+)]

A CD19 H-score of zero was considered negative.

Revised IWG Response Criteria for Malignant Lymphoma[2]

Complete Remission (CR): CR requires all of the following:

- Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.
- Typically FDG-avid lymphoma (large cell, mantle cell and follicular lymphomas are all typically FDG-avid): in subjects with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.
- Variably FDG-avid lymphomas/FDG avidity unknown: in subjects without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed to normal size (≤ 1.5 cm in greatest diameter if > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1 cm in their short axis before treatment must have decreased to ≤ 1.0 cm in their short axis after treatment.
- The spleen and/or liver, if considered to be enlarged before therapy on basis of physical exam or CT scan, must should be normal size on CT scan and not be palpable on physical examination and nodules thought to represent lymphoma must no longer be present.
- A bone marrow aspirate and biopsy is performed only when the patient had bone marrow involvement with lymphoma prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow

involvement with lymphoma after treatment. The bone marrow aspirate and biopsy must show no evidence of disease by morphology or if indeterminate by morphology it must be negative by immunohistochemistry. The biopsy core sample must be a minimum of 20 mm in length.

Partial Remission (PR): PR requires all of the following:

- ≥ 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. Dominant nodes or nodal masses should be clearly measurable in at least 2 perpendicular dimensions, should be from different regions of the body if possible and should include mediastinal and retroperitoneal nodes if possible.
- No increase in size of nodes, liver or spleen and no new sites of disease.
- If multiple splenic and hepatic nodules are present, they must regress by ≥ 50% in the SPD. There must be a > 50% decrease in the greatest transverse diameter for single nodules.
- Bone marrow is irrelevant for determination of a PR. If patient has persistent bone marrow involvement and otherwise meets criteria for CR the patient will be considered a PR.
- Typically FDG-avid lymphoma: for subjects with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET scan should be positive in at least one previously involved site. Note: in subjects with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated in subjects with one or at most two residual masses that have regressed by 50% on CT scan.

Stable Disease (SD):

- Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. PET should be positive in typically FDG-avid lymphomas.

Progressive Disease (PD, defined by at least one of the following):

- ≥ 50% increase from nadir in the sum of the products of at least two lymph nodes, or if a single node is involved at least a 50% increase in the product of the diameters of this one node.
- Appearance of a new lesion greater than 1.5 cm in any axis even if other lesions are decreasing in size
- Greater than or equal to a 50% increase in size of splenic or hepatic nodules
- At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.
- Lesions should be PET positive in typically FDG-avid lymphomas unless the lesion is too small to be detected by PET (<1.5 cm in its long axis by CT)

PET Disease staging

Baseline PET-CT scans of the neck, chest, abdomen, pelvis, as well as other appropriate disease sites were required. Patients had their first post–axi-cel PET-CT at 4 weeks after infusion, at month 3 and every 3 months thereafter up to 2 years post–axi-cel infusion. After 2 years, PET-CT scans were performed as clinically indicated and/or per the institution's standard of care. A negative FDG-PET scan based on a Deauville Five-Point Scale (5PS) score of 1, 2, or 3 was a requirement for complete response.[3,4] As applicable, a negative bone marrow aspirate/biopsy was required to confirm complete response (i.e., for patients presenting with bone marrow involvement prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment).

The designation of Complete Metabolic Response (CMR) for the ZUMA-1 study required all of the following:

1. A 5PS score of 1, 2, or 3, with or without a residual mass. Non-index lesion 5PS score of 1, 2 or 3
2. No new sites of disease observed

Additionally, in the event the screening FDG-PET scan was missing, and the on-study index and non-index 5PS score was a 1, 2, or 3, then a response of CMR was possible.

In Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow, uptake was allowed to be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response was allowed to be assigned by the reader if uptake at sites of initial involvement was no greater than surrounding normal tissue even if the tissue had high physiologic uptake.

Toxicity management

Cytokine release syndrome (CRS) grading and treatment recommendations were adapted from Lee, et al.[5] Neurologic events were graded per CTCAE and defined consistent with the blinatumomab registrational study.[6] Events were coded using the MedDRA version 18.1 consisting of select items in both the Nervous Systems Disorders and Psychiatric Disorders System Organ Class. Baseline brain magnetic resonance imaging (MRI) was required at time of screening. Clinical neurologic assessment and Mini-Mental State Evaluation (MMSE) were performed at baseline and every other day while patients were hospitalized. CRS and neurological events were managed per protocol defined treatment guidelines outlined below.

Cytokine Release Syndrome Grading Assessment	Extensive co-morbidities or older age? No/Yes	Treatment
Grade 1: • Fever (defined as ≥ 38.3°C) • Constitutional symptoms	N/A	• Vigilant supportive care • Assess for infection • Treat fever and neutropenia if present, monitor fluid balance, antipyretics, analgesics as needed
Grade 2: • Hypotension: responds to fluids or one low dose vasopressor • Hypoxia: responds to < 40% O^2 • Organ toxicity: grade 2	No	• As above for grade 1 • Monitor organ function closely • Monitor with continuous cardiac telemetry and pulse oximetry
Grade 2: • Hypotension: responds to fluids or one low dose vasopressor • Hypoxia: responds to < 40% O^2 • Organ toxicity: grade 2	Yes	• Consider tocilizumab (8 mg/kg IV over 1 hour, not to exceed 800 mg) ± corticosteroids (e.g., methylprednisolone 1 mg/kg BID or dexamethasone 10 mg every 6 hours)
Grade 3: • Hypotension: requires multiple vasopressors or high-dose vasopressors • Hypoxia: requires ≥ 40% O^2 • Organ toxicity: grade 3 **or** grade 4 transaminitis	N/A	
Grade 4 • Mechanical ventilation • Organ toxicity: grade 4 excluding transaminitis	N/A	• As above for grade 2/3 • Corticosteroids (e.g., methylprednisolone 1g/day × 3, followed by a rapid taper consisting of 250 mg BID × 2 days, 125 mg BID × 2 days and then 60 mg BID × 2 days)

BID, twice daily; IV, intravenously; N/A, not applicable.

Neurotoxicity Grading assessment (CTCAE 4.03)	Treatment	Evaluation
Grade 1: Examples include: • Somnolence-mild drowsiness or sleepiness • Confusion-mild disorientation • Encephalopathy-mild limiting of ADL • Dysphasia-not impairing ability to communicate • Brief partial seizure; no loss of consciousness	• Vigilant supportive care	• Neurological examination • Additional work up as clinically indicated
Grade 2: Examples include: • Somnolence-moderate, limiting instrumental ADL • Confusion-moderate disorientation, limiting instrumental ADL • Encephalopathy-limiting instrumental ADL • Dysphasia-moderate impairing ability to communicate spontaneously • Brief generalized seizure	• Vigilant supportive care • Consider tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg)	• Should include brain MRI and evaluation of CSF in addition to neurological exam • Consider EEG as clinically indicated
Grade 3: Examples include: • Somnolence-obtundation or stupor • Confusion-severe disorientation, limiting self-care ADL • Encephalopathy-limiting self- care ADL • Dysphasia-severe receptive or expressive characteristics, impairing ability to read, write or communicate intelligibly • Multiple seizures despite medical intervention • Weakness limiting self-care ADL; disabling • Complete bowel/bladder incontinence	• **As per above for grade 2** • Repeat tocilizumab, 8 mg/kg IV over 1 hour (not to exceed 800 mg), every 4-6 hours if symptoms have not stabilized or improved within 12-24 hours • Consider corticosteroids (e.g., dexamethasone 10 mg IV every 6 hours, methylprednisolone 1 mg/kg BID) for worsening symptoms despite tocilizumab	• **As above for grade 2** • **Monitor with continuous cardiac telemetry and pulse oximetry**
Grade 4: • Life-threatening consequences • Urgent Intervention Indicated • Mechanical ventilation • Life-threatening; prolonged repetitive seizures	• **As per above for grade 2/3** • Corticosteroids (e.g., methylprednisolone 1 g/day × 3, followed by a rapid taper consisting of 250 mg BID × 2 days, 125 mg BID × 2 days and then 60 mg BID × 2 days)	

ADL, activities of daily living; BID, twice daily; CSF, cerebrospinal fluid; EEG, electroencephalogram; IV, intravenously; MRI, magnetic resonance imaging.

Immunogenicity

Patients were evaluated for immunogenicity following CAR T cell therapy using an enzyme-linked immunosorbent assay (ELISA) for the detection of binding antibodies against FMC63, the originating antibody of the anti-CD19 CAR.

Retreatment

Retreatment with axi-cel was allowed under certain conditions in ZUMA-1 in order to further explore the risk:benefit of a subsequent treatment of axi-cel upon progression. Prior to retreatment with axi-cel, the patient would receive a second course of conditioning chemotherapy consistent with the treatment schedule for the first dose. Per protocol, patients needed to be eligible for retreatment, including evidence of CD19 tumor expression as described below:

A patient was eligible for retreatment with axi-cel under the following conditions:

- Patient had a PR or CR at the month 3 disease assessment
- Patient's disease subsequently progressed greater than 3 months after axi-cel infusion
- CD19 tumor expression was confirmed locally by biopsy after disease progression and prior to re-treatment
- The patient continues to meet the original study eligibility criteria with exception of prior axi-cel use in this study
- The patient has not received subsequent therapy for the treatment of lymphoma
- The patient did not experience a dose-limiting toxicity in phase 1 or a comparable toxicity in phase 2
- Toxicities related to conditioning chemotherapy (fludarabine and cyclophosphamide), with the exception of alopecia, have resolved to ≤ grade 1 or returned to baseline prior to re-treatment

- The patient does not have known neutralizing antibodies, the exception being that if non-neutralizing human anti-mouse antibody (HAMA) or human anti-bovine antibody (HABA) develop, the patient may be retreated if they meet the original study eligibility criteria

Statistical analyses

Prior to the primary analysis, protocol-specified interim futility and efficacy analyses were conducted after 20 and 50 cohort 1 patients, respectively, were evaluable with 3 months of follow-up and reviewed by the Data Safety Monitoring Board.

Duration of response or complete response was defined as the date of a patient's first objective response or complete response, respectively, until the time of disease progression per the revised IWG Response Criteria for Malignant Lymphoma[2] or death regardless of cause.

The follow-up for overall survival is defined as the time from axi-cel infusion to the data-cutoff date.

The 2-sided 95% confidence intervals for median duration of response, progression-free survival, and overall survival (Figure 2) were calculated using Kaplan-Meier plots and estimates.

Supplementary Figures and Tables

Figure S1. Consort Diagram for Overall Population (N=111).

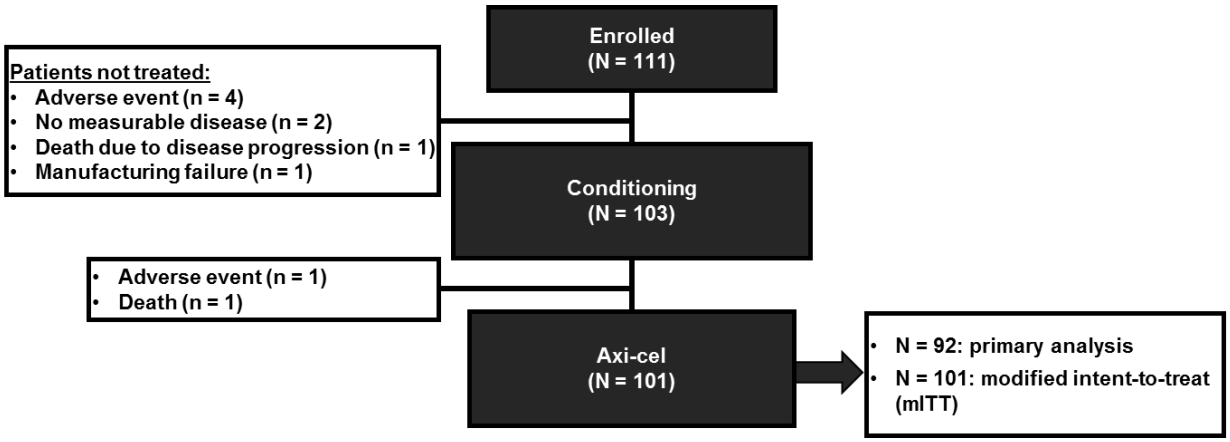

Figure S2. Representative PET Scans of Complete Response. The images show a 62-year-old male who had previously received 4 lines of systemic therapy: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); rituximab, gemcitabine, dexamethasone, and cisplatin (R-GDP); rituximab, ifosfamide, carboplatin, and etoposide (R-ICE); and rituximab plus lenalidomide. The patient had multi-compartmental lymphadenopathy and lung masses at study entry. Following therapy with axi-cel, he achieved a complete response at 3 months and remains in complete remission 18 months later.

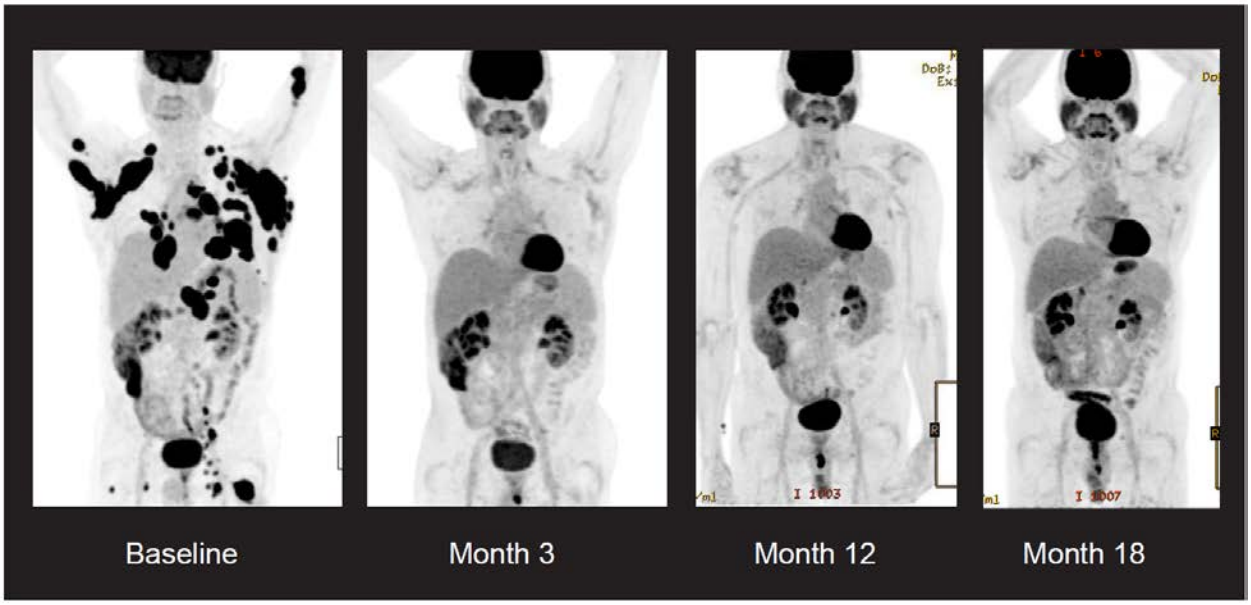

Figure S3. Subgroup Analysis of Ongoing Responses at 12 Months. The panel shows the subgroup analysis of the rate of ongoing responses for key baseline and clinical covariates. * Indicates the number of evaluable patients. † The 95% lower confidence interval (LCI) and upper confidence interval (UCI) of the ongoing response rate were calculated using the Clopper-Pearson method.

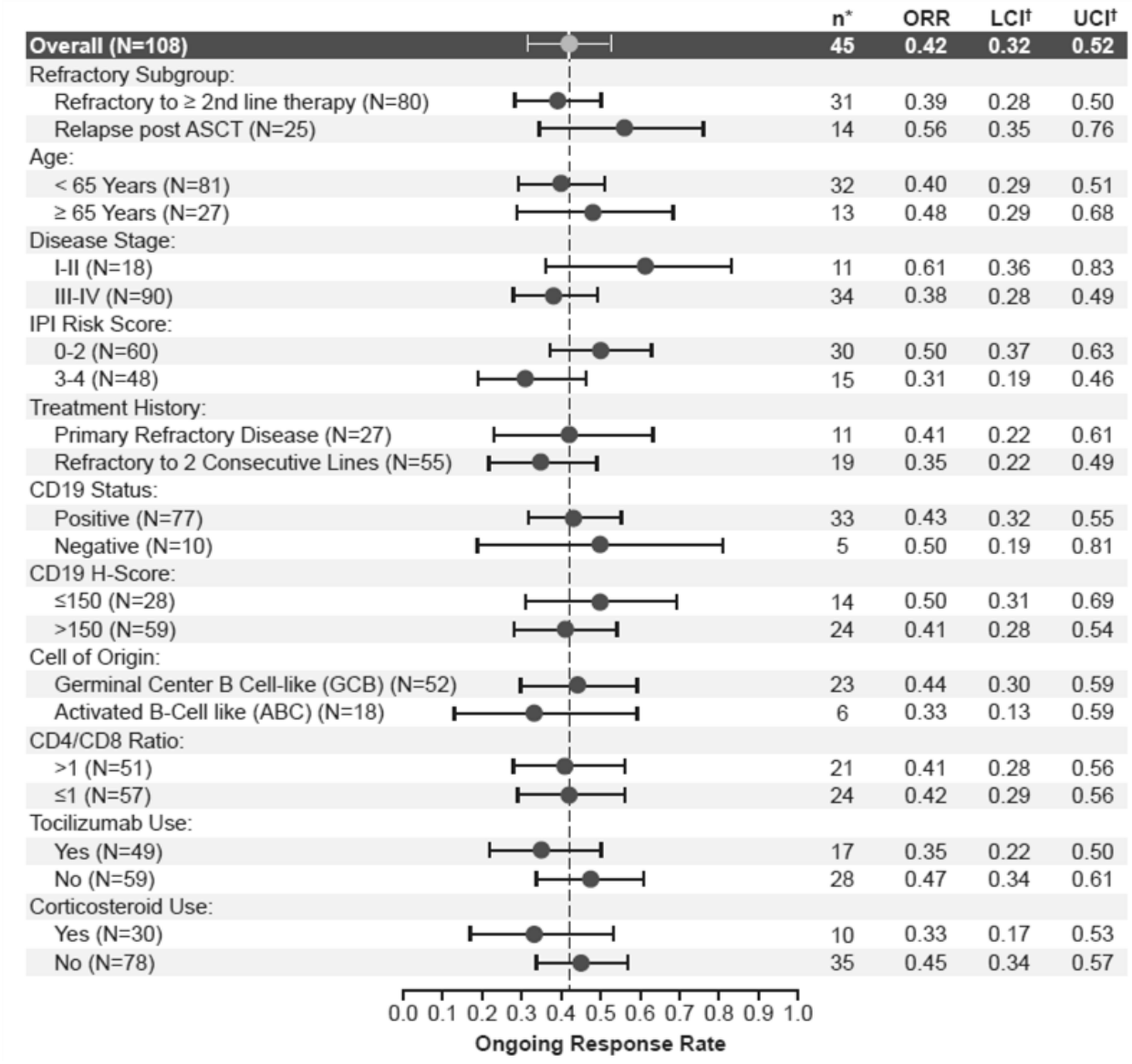

Figure S4. Axi-cel Correlations With Response and Adverse Events by Area Under the Curve (AUC). The panel shows the association of CAR T-cell expansion with objective response rate (ORR), neurologic events (NE), and cytokine release syndrome (CRS). CAR AUC is defined as cumulative levels of CAR+ cells/µL of blood over the first 28 days post axi-cel. AUC fold change is shown for patients with vs. without response, grade ≥3 vs. grades 0-2 NE, or grade ≥3 vs. grades 0-2 CRS. P values were calculated by Wilcoxon rank sum test.

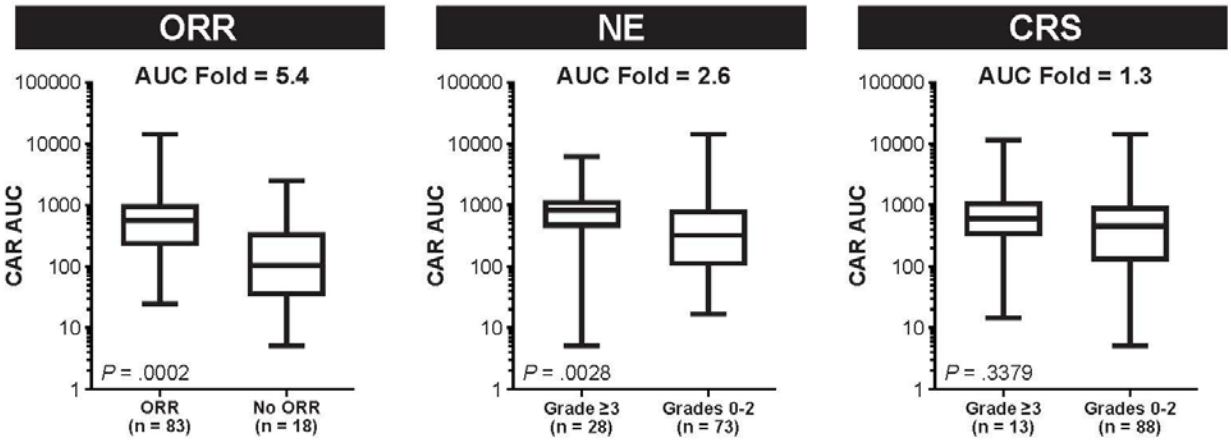

Table S1. Best Overall Response Based on Investigator Assessment of the Primary Analysis Population.

Response — no. (%)	DLBCL (n = 72)	PMBCL/TFL (n = 20)	All Patients (N = 92)
Objective response rate	58 (81)	17 (85)	75 (82)
Complete response	34 (47)	14 (70)	48 (52)
Partial response	24 (33)	3 (15)	27 (29)
Stable disease	9 (13)	2 (10)	11 (12)

Table S2. Best and Ongoing Response by Cell of Origin.

Response — no. (%)	ABC (n = 17)	GCB (n = 49)
Objective response rate	13 (76)	43 (88)
Complete response	10 (59)	28 (57)
Ongoing response	6 (35)	23 (47)

ABC, activated B cell; GCB, germinal center B cell.

Table S3. Distribution of T Cell Phenotypes in Axi-cel Product.

T Cell Phenotypes	Median (range), %
T_N (CCR7+ and CD45RA+)	13.9 (1.0 – 76.0)
T_{CM} (CCR7+ and CD45RA-)	26.1 (9.0 – 50.1)
T_{EM} (CCR7- and CD45RA-)	37.9 (5.1 – 70.4)
T_{EFF} (CCR7- and CD45RA+)	15.4 (4.7 – 39.1)
(% T_N + % T_{CM})/(% T_{EM} + % T_{EFF})	0.7 (0.2 – 5.7)

T_{CM}, central memory cells; T_{EFF}, effector cells; T_{EM}, effector memory cells; T_N, naïve cells.

Table S4. Best Response and Grade ≥3 Neurologic Events and Cytokine Release Syndrome by CD4:CD8 Ratio and T Cell Subsets in Axi-cel Products Infused.

	ORR	CR	Grade ≥3 Neurologic Events	Grade ≥3 Cytokine Release Syndrome
Overall (N = 101), %	**82**	**54**	**28**	**13**
Product Characteristics				
CD4:CD8 Ratio				
Evaluable, N	96	96	97	97
Min – Q1, % (0.03-0.5)	92	68	32	16
Q1 – Median,% (0.5-0.9)	67	46	50	13
Median – Q3, % (0.9-1.9)	83	50	21	13
Q3 – Max, % (1.9-5.8)	92	54	13	13
(T_N+T_{CM})/(T_{EM}+T_{EFF}) Ratio				
Evaluable, N	96	96	97	97
Min – Q1, % (0.2 – 0.5)	84	52	44	16
Q1 – Median, % (0.5 – 0.7)	83	54	38	8
Median – Q3, % (0.7 – 1.3)	79	54	17	13
Q3 – Max, % (1.3 – 5.7)	88	58	17	17

CR, complete response; ORR, objective response rate; T_{CM}, central memory cells; T_{EFF}, effector cells; T_{EM}, effector memory cells; T_N, naïve cells. Median CD4:CD8 ratio was 0.87.

Table S5. Adverse Event Rates at Interim and Primary Analyses for the Modified Intent-to-treat (mITT) Population. Rates of grade ≥3 adverse events (AE) cytokine release syndrome (CRS) and neurologic events (NE) decreased during the course of the study, comparing the first 62 patients at interim analysis vs. all 101 patients for the mITT analysis.

Adverse event — no. (%)	Interim Analysis (N = 62)	mITT Analysis (N = 101)
Grade ≥3 AE	59 (95)	96 (95)
Grade ≥3 CRS	11 (18)	13 (13)
Grade ≥3 NE	21 (34)	28 (28)

Table S6. New-onset Treatment-emergent Serious Adverse Events (SAEs; excluding adverse events after disease progression or subsequent new therapy) Occurring in Patients Alive After Primary Analysis Data Cut-off.

Patient	SAE Start Time Post Axi-cel Infusion (months)	Grade	SAE
1	8.7	3	Lung infection
2	16.7	3	Recurrent viral upper respiratory infection
	18.6	3	Rotavirus infection
3*	12.5	3	Pneumonia
4	7.2	4	Sepsis
	7.2	3	Left lower lobe pneumonia
	7.2	3	Atrial fibrillation with rapid ventricular response
5	9.1	3	Lung infection
	9.2	3	Febrile neutropenia
6	7.1	3	Influenza B infection
7	7.9	3	Infection other - pneumonia
8	6.7	1	Muscle weakness right side
	6.7	2	Slurred speech
9†	9.3	3	Heart failure
10	14.4	3	Community acquired pneumonia

*****Patient 3 had an SAE on Day 379 within 14 days of disease progression which occurred on Day 365.

†Patient 9 achieved a complete response followed by disease progression, then was retreated with axi-cel and underwent allogeneic stem cell transplant while in second complete response. The investigator attributed the SAE of heart failure to the myeloablative chemotherapy and antithymocyte globulin administered during conditioning for allogeneic stem cell transplant.

Table S7. Best Response and Grade ≥3 Neurologic Events and Cytokine Release Syndrome by Peak CAR T-cell Expansion

	ORR	CR	Grade ≥3 Neurologic Events	Grade ≥3 Cytokine Release Syndrome
Overall (N = 101), %	**82**	**54**	**28**	**13**
CAR T $AUC_{Day\ 0-28}$				
Evaluable, N	94	94	96	96
Min – Q1, % (5.1 – 147.6)	58	25	13	8
Q1 – Median, % (147.6 – 462.3)	79	58	17	13
Median – Q3, % (462.3 – 930.4)	96	71	42	13
Q3 – Max, % (930.4 – 14,329.3)	96	63	42	17

AUC, area under the curve; CR, complete response; ORR, objective response rate.

Table S8. Association of Serum Biomarkers With Cytokine Release Syndrome and Neurologic Events.

		Cytokine Release Syndrome			Neurologic Events		
Function	**Peak Value — Median (range), pg/mL**	**Grade ≥3**	**Grade 0-2**	***P* Value**	**Grade ≥3**	**Grade 0-2**	***P* Value**
		(n = 13)	**(n = 88)**		**(n = 28)**	**(n = 73)**	
Homeostatic/ proliferative	IL-15	78.6 (31.≥25, 210.6)	48.2 (11.3, 226.6)	0.0462	70.7 (27.7, 210.6)	43.6 (11.3, 226.6)	0.0001
Pro-inflammatory	IL-6	713.9 (152.5, 5070.5)	49.4 (3.5, 12109.7)	0.0008	302.5 (26.6, 12109.7)	36.1 (3.5, 1386.9)	0.0000
	IL-1Ra	4000.0 (1263.4, 40000.0)	2074.1 (510.8, 40000.0)	0.0526	3261.0 (814.6, 40000.0)	2052.8 (510.8, 14781.9)	0.0183
	IL-2Rα	22122.3 (7878.4, 100000.0)	10994.8 (78.0, 71859.4)	0.0462	17865.3 (4586.8, 90484.3)	10511.5 (78.0, 100000.0)	0.0363
Immune-modulating	IFNγ	955.4 (249.1, 8209.2)	366.7 (7.5, 7058.9)	.0462	995.5 (97.2, 8209.2)	350.8 (7.5, 2585.1)	0.0043
	IL-10	124.7 (23.7, 466.0)	28.3 (0.7, 466.0)	.0196	82.7 (6.2, 466.0)	25.5 (0.7, 466.0)	0.0155
Chemokines	IL-8	495.5 (25.9, 1260.0)	81.0 (9.8, 2664.4)	.0603	274.6 (37.0, 2664.4)	68.3 (9.8, 750.0)	0.0004
	CCL-2	1500 (1209.4, 1500)	1359.1 (428.8, 1500)	0.0610	1500 (766.5, 1500)	1249.6 (428.8, 1500)	0.0036
Effector	Granzyme B	55.6 (7.7, 1005.7)	19.6 (1.0, 3306.0)	.0462	41.2 (5.3, 3306.0)	17.8 (1.0, 1005.7)	0.0363

Table S9. Best Overall Response Based on Investigator Assessment of the Intent-to-treat Population at the Primary Analysis Data Cut-off.

Response — no. (%)	**DLBCL (n = 81)**	**PMBCL/TFL (n = 30)**	**All Patients (N = 111)**
Objective response rate	63 (78)	22 (73)	85 (77)
Complete response	38 (47)	19 (63)	57 (51)
Partial response	25 (31)	3 (10)	28 (25)
Stable disease	9 (11)	2 (7)	11 (10)

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