Supplementary Appendix

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

Supplementary Appendix

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ZUMA-7 Study Team

Study Team Member	Site
Investigators	
Avivi, Irit, M.D.	Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
Bachy, Emmanuel, M.D. Former: Salles, Gilles, M.D.	Centre Hospitalier Lyon Sud, Pierre Benite, France
Caballero, Dolores, M.D.	Hospital Universitario de Salamanca, Salamanca, Spain
Canales, Miguel, M.D.	University Hospital La Paz, Madrid, Spain
Carabasi, Matthew, M.D.	Sidney Kimmel Cancer Center, Philadelphia, Pennsylvania, United States
Castro, Januario, M.D.	Mayo Clinic – Arizona, Phoenix, Arizona, United States
Chaganti, Sridhar, M.D.	University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom
Cunningham, David, M.D.	The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom
Cwynarski, Katherine, M.D.	University College London NHS Foundation Trust, London, United Kingdom
Davison, Kelly, M.D.	McGill University, Montreal, Quebec, Canada
de Vos, Sven, M.D.	University of California, Los Angeles, Santa Monica, California, United States
Deol, Abhinav, M.D.	Karmanos Cancer Institute, Detroit, Michigan, United States
Dickinson, Michael, M.D.	Peter MacCallum Cancer Center, Melbourne, Australia
Dorritie, Kathleen, M.D.	University of Pittsburg Medical Center, Pittsburg, Pennsylvania, United States
Dreger, Peter, M.D.	Universitaetsklinikum Heidelberg, Heidelberg, Germany
Elsawy, Mahmoud, M.D.	Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada
Enblad, Gunilla, M.D.	Uppsala Akademiska Hospital, Uppsala, Sweden
Farooq, Umar, M.D.	University of Iowa Hospitals and Clinics, Iowa City, Iowa, United States
Ferreri, Andrés José María, M.D.	Ospedale San Raffaele, Milano, Italy

Fleury, Isabelle, M.D.	Hôpital Maisonneuve – Rosemont, Montreal, Quebec, Canada
Flinn, Ian, M.D., Ph.D.	Sarah Cannon – Tennessee, Nashville, Tennessee, United States
Ghobadi, Armin, M.D.	Washington University School of Medicine, St. Louis, Missouri, United States
Greinix, Hildegard, M.D.	Medizinische Universitaet Graz, Graz, Austria
Hallam, Simon, M.D.	St. Bartholomew's Hospital, London, United Kingdom
Hill, Brian, M.D., Ph.D.	Cleveland Clinic – Taussig Cancer Institute, Cleveland, Ohio, United States
Houout, Roch, M.D. Former: De Guibert, Sophie, M.D.	CHU de Rennes-Hôpital Pontchaillou, Rennes, France
Jacobson, Caron, M.D.	Dana Farber Cancer Institute, Boston, Massachusetts, United States
Jaglowski, Samantha, M.D.	Ohio State University, Columbus, Ohio, United States
Jerkeman, Mats, M.D.	Lunds Universitet, Lund, Sweden
Johnston, Patrick, M.D., Ph.D.	Mayo Clinic, Rochester, Minnesota, United States
Karmali, Reem, M.D.	Northwestern University Feinberg School of Medicine, Chicago, Illinois, United States
Kennah, Mike, M.D. Former: Kekre, Natasha, M.D.	Ottawa Hospital – General Campus, Ottawa, Ontario, Canada
Kersten, Marie José, M.D., PhD	Amsterdam University Medical Centers, Amsterdam, Netherlands
Kröger, Nicolaus, M.D.	Universitaetsklinikum Hamburg-Eppendorf Klinik und Poliklinik fuer Innere Medizin, Hamburg, Germany
Kuruvilla, John, M.D.	Princess Margaret Cancer Centre, Toronto, Ontario, Canada
Larouche, Jean François, M.D.	Hôpital de l'Enfant-Jesus, Quebec, Quebec, Canada
Le Gouill, Steven, M.D.	CHU de Nantes – Hôtel Dieu, Nantes, France
Lee, Catherine, M.D. Former: Stephens, Deborah, M.D.	Huntsman Cancer Institute, Salt Lake City, Utah, United States
Lekakis, Lazaros, M.D.	University of Miami, Miami, Florida, United States

Leslie, Lori, M.D.	Hackensack University Medical Center, Hackensack, New Jersey, United States
Locke, Frederick, M.D.	Moffitt Cancer Center, Tampa, Florida, United States
Lopez-Guillermo, Armando, M.D.	Hospital Clinic de Barcelona, Barcelona, Spain
Lugtenburg, Pieternella, M.D.	Erasmus MC, Rotterdam, Netherlands
McGuirk, Joseph, D.O.	University of Kansas Cancer Center, Westwood, Kansas, United States
Mehta, Amitkumar, M.D.	University of Alabama Comprehensive Cancer Center, Birmingham, Alabama, United States
Miklos, David, M.D., Ph.D.	Stanford University, Palo Alto, California, United States
Minnema, Monique, M.D.	Universitair Medisch Centrum Utrecht, Utrecht, Netherlands
Morschhauser, Franck, M.D.	CHRU de Lille-Hôpital Claude Huriez, Lille, France
Muller, Antonia, M.D.	Universitaets-Spital Zurich Clinical Trials Center, Zurich, Switzerland
Oluwole, Olalekan, M.D.	Vanderbilt University, Nashville, Tennessee, United States
Osman, Keren, M.D.	Icahn School of Medicine at Mount Sinai, New York, New York, United States
Pagel, John, M.D., Ph.D.	Swedish Cancer Institute, Seattle, Washington, United States
Panizo Santos, Carlos, M.D.	Clínica Universidad de Navarra, Pamplona, Spain
Perales, Miguel-Angel, M.D.	Memorial Sloan-Kettering, New York, New York, United States
Poire, Xavier, M.D.	Cliniques Universitaires Saint-Luc, Brussels, Belgium
Portell, Craig, M.D.	University of Virginia, Charlottesville, Virginia, United States
Radford, John, M.D.	The Christie NHS Foundation Trust, Manchester, United Kingdom
Rapoport, Aaron, M.D.	University of Maryland St. Joseph Medical Center, Baltimore, Maryland, United States
Reagan, Patrick, M.D.	University of Rochester, Rochester, New York, United States

Riedell, Peter, M.D.	University of Chicago, Chicago, Illinois, United States
Rudzki, Jakob, M.D.	Medizinische Universitaet Innsbruck – Universitaetsklinik fuer Innere Medizin V, Innsbruck, Austria
Song, Kevin, M.D.	Vancouver General Hospital, Vancouver, British Columbia, Canada
Stadelmann, Raphael, M.D.	Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland
Stelljes, Matthias, M.D.	Universitaetsklinikum Muenster, Medizinische Klinik A, Muenster, Germany
Sureda Balari, Anna, M.D.	Institut Catala d'Oncologia, Barcelona, Spain
Szwajcer, David, M.D.	CancerCare Manitoba, Winnipeg, Manitoba, Canada
Thieblemont, Catherine, M.D.	Hôpital Saint-Louis, Paris, France
Topp, Max, M.D.	Universitaetsklinikum Wuerzburg, Wuerzburg, Germany
Tzachanis, Dimitrios, M.D. Former: Castro, Januario, M.D.	University of California, San Diego, La Jolla, California, United States
Ulrickson, Matthew, M.D. Former: Muñoz, Javier, M.D.	Banner MD Anderson Cancer Center, Gilbert, Arizona, United States
van Meerten, Tom, M.D.	University Medical Center Groningen, Groningen, Netherlands
Vandenberghe, Peter, M.D., Ph.D.	Universitair Ziekenhuis Leuven, Leuven, Belgium
Wannesson, Luciano, M.D.	Instituto Oncologico Della Svizzera Italiana (IOSI), Bellinzona, Switzerland
Wermke, Martin, M.D.	Universitaetsklinikum Carl Gustav Carus Dresden, Dresden, Germany
Westin, Jason, M.D.	MD Anderson Cancer Center, Houston, Texas, United States
Wulf, Gerald, M.D.	Universitaetsmedizin Goettingen, Goettingen, Germany
Zinzani, Pier Luigi, M.D.	Policlinico S.Orsola-Malpighi, Bologna, Italy
Kite Members (Past and Present) and Sub-Investigators	
Advani, Ranjana, M.D.	Stanford University, Palo Alto, California, United States
Afonso-Smith, Suzanne	Kite, Santa Monica, California, United States
Agopyan, Nadia, Ph.D.	Kite, Santa Monica, California, United States
Ahern, Janet	Kite, Santa Monica, California, United States

Atienza, Anna	Kite, Santa Monica, California, United States
Audzevich, Tatsiana, Ph.D.	Kite, Santa Monica, California, United States
Brock, Katie	Kite, Santa Monica, California, United States
Brothers, Julie	Kite, Santa Monica, California, United States
Chavez, Julio, M.D.	Moffitt Cancer Center, Tampa, Florida, United States
Chonzi, David, M.D.	Kite, Santa Monica, California, United States
Cohen, Alexa	Kite, Santa Monica, California, United States
Dahiya, Saurabh, M.D.	University of Maryland St. Joseph Medical Center, Baltimore, Maryland, United States
Dixon, Ellen	Kite, Santa Monica, California, United States
Doan, Thu, Pharm.D.	Kite, Santa Monica, California, United States
Fisher, Cailin	Kite, Santa Monica, California, United States
Go, William, M.D., Ph.D.	Kite, Santa Monica, California, United States
Goulding, Mike	Kite, Santa Monica, California, United States
Hacker, Jill	Kite, Santa Monica, California, United States
Hale, Robert	Kite, Santa Monica, California, United States
Houghton, Geoff	Kite, Santa Monica, California, United States
Jiang, Yizhou, Ph.D.	Kite, Santa Monica, California, United States
Kang, Janet, Pharm.D.	Kite, Santa Monica, California, United States
Kennedy, Audrey	Kite, Santa Monica, California, United States
Kerber, Anne, M.D.	Kite, Santa Monica, California, United States
Lee, Lillian	Kite, Santa Monica, California, United States
Malladi, Ram, M.D.	Cambridge University, England
Manufacturing and Quality Team Members	Kite, Santa Monica, California, United States
Marfori, Lindsey	Kite, Santa Monica, California, United States
McLeroy, Jeffrey, M.D.	Kite, Santa Monica, California, United States
Mercado, Charles	Kite, Santa Monica, California, United States
Miao, Harry, M.D.	Kite, Santa Monica, California, United States
Nastoupil, Loretta, M.D.	MD Anderson Cancer Center, Houston, Texas, United States
Navale, Lynn	Kite, Santa Monica, California, United States

Nicholson, Emma, PhD	The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom
Peng, Andrew	Kite, Santa Monica, California, United States
Purdum, Anna, Pharm.D.	Kite, Santa Monica, California, United States
Rahimi, Golnaz	Kite, Santa Monica, California, United States
Rodgers, Beth	Kite, Santa Monica, California, United States
Rossi, John	Kite, Santa Monica, California, United States
Sherman, Marika	Kite, Santa Monica, California, United States
Sherman, Sarah	Kite, Santa Monica, California, United States
Sleer, Leanne, Ph.D.	Kite, Santa Monica, California, United States
Snider, Julia Thornton, Ph.D.	Kite, Santa Monica, California, United States
Squires, Amanda	Kite, Santa Monica, California, United States
Stockdale, Dan	Kite, Santa Monica, California, United States
Techau, Jared	Kite, Santa Monica, California, United States
Tricker, Erin, Ph.D.	Kite, Santa Monica, California, United States
Vardhanabhuti, Saran, Ph.D.	Kite, Santa Monica, California, United States
Vella, Laura	Kite, Santa Monica, California, United States
Vezan, Remus, M.D., Ph.D.	Kite, Santa Monica, California, United States
Villarreal, Rebeca	Kite, Santa Monica, California, United States
Wallace, Joanne, Ph.D.	Kite, Santa Monica, California, United States
Wang, Paul, Pharm.D.	Kite, Santa Monica, California, United States
Wiezorek, Jeffrey, M.D.	Kite, Santa Monica, California, United States
Xue, Allen, Ph.D.	Kite, Santa Monica, California, United States

Supplementary Methods

Eligibility criteria

Additional inclusion criteria:

- Histologically proven large B-cell lymphoma including the following types defined by World Health Organization 2016[1]
    - Diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including activated B-cell–like [ABC]/germinal center B-cell–like [GCB])
    - High grade B-cell lymphoma with or without *MYC* and *B-cell lymphoma 2 (BCL2)* and/or *BCL6* rearrangement
    - DLBCL arising from follicular lymphoma
    - T-cell/histiocyte-rich large B-cell lymphoma
    - DLBCL associated with chronic inflammation
    - Primary cutaneous DLBCL, leg type
    - Epstein-Barr virus + DLBCL
- Relapsed or refractory disease after first-line chemoimmunotherapy
    - Refractory disease defined as no complete remission to first-line therapy; patients who were intolerant to first-line therapy were excluded
        - Progressive disease (PD) as best response to first-line therapy
        - Stable disease (SD) as best response after at least four cycles of first-line therapy (e.g., 4 cycles of rituximab-cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone)
        - Partial response (PR) as best response after at least six cycles and biopsy-proven residual disease or disease progression ≤12 months of therapy
    - Relapsed disease defined as complete remission to first-line therapy followed by biopsy-proven disease relapse ≤12 months of first-line therapy
- Patients must have received adequate first-line therapy including at a minimum:
    - Anti-CD20 monoclonal antibody unless investigator determines that tumor is CD20 negative, and
    - An anthracycline containing chemotherapy regimen
- Intended to proceed to high-dose therapy with autologous stem cell transplant (HDT-ASCT) if response to second-line therapy

- Patients must have had radiographically documented disease
- No known history or suspicion of central nervous system (CNS) involvement by lymphoma
- At least two weeks or five half-lives, whichever is shorter, must have had elapsed since any prior systemic cancer therapy at the time the patient provides consent
- Age 18 years or older at the time of informed consent
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Adequate bone marrow, renal, hepatic, pulmonary, and cardiac function defined as:
    - Absolute neutrophil count ≥1000/μl
    - Platelet count ≥75,000/μl
    - Absolute lymphocyte count ≥100/μl
    - Creatinine clearance (as estimated by Cockcroft Gault) ≥60 ml/min
    - Serum alanine aminotransferase/aspartate aminotransferase ≤2.5 upper limit of normal
    - Total bilirubin ≤1.5 mg/dl, except in patients with Gilbert's syndrome
    - Cardiac ejection fraction ≥50%, no evidence of pericardial effusion as determined by an echocardiogram, and no clinically significant electrocardiogram findings
    - No clinically significant pleural effusion
    - Baseline oxygen saturation >92% on room air
- Females of childbearing potential must have a negative serum or urine pregnancy test (females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years were not considered to be of childbearing potential)

Additional exclusion criteria:

- History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (e.g., cervix, bladder, breast) unless disease free for at least 3 years
- History of Richter's transformation of chronic lymphocytic leukemia or primary mediastinal large B-cell lymphoma
- History of autologous or allogeneic stem cell transplant
- Received more than one line of therapy for DLBCL
- Prior CD19 targeted therapy
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin-2) within six weeks or five half-lives of the drug, whichever is

shorter, prior to the first dose of axicabtagene ciloleucel (axi-cel) or standard of care (SOC)

- Prior chimeric antigen receptor (CAR) therapy or other genetically modified T-cell therapy or prior randomization into ZUMA-7
- History of severe, immediate hypersensitivity reaction attributed to aminoglycosides
- Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring intravenous (IV) antimicrobials for management. Simple urinary tract infection and uncomplicated bacterial pharyngitis are permitted if responding to active treatment
- Known history of infection with human immunodeficiency virus (HIV) or hepatitis B (HBsAg positive) or hepatitis C virus (anti-HCV positive). If there is a positive history of treated hepatitis B or hepatitis C, the viral load must be undetectable per quantitative polymerase chain reaction (PCR) and/or nucleic acid testing
- Active tuberculosis
- Presence of any indwelling line or drain (e.g., percutaneous nephrostomy tube, indwelling Foley catheter, biliary drain, or pleural/peritoneal/pericardial catheter). Dedicated central venous access catheters, such as a port-a-cath or Hickman catheter, are permitted
- Patients with detectable cerebrospinal fluid malignant cells or known brain metastases or with a history of cerebrospinal fluid malignant cells or brain metastases
- History or presence of non-malignant CNS disorder, such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement
- Patients with cardiac atrial or cardiac ventricular lymphoma involvement
- History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, New York Heart Association Class II or greater congestive heart failure, or other clinically significant cardiac disease within 12 months of enrollment
- Requirement for urgent therapy due to tumor mass effects, such as bowel obstruction or blood vessel compression
- History of autoimmune disease requiring systemic immunosuppression and/or systemic disease modifying agents within the last 2 years
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active

pneumonitis per chest computed tomography (CT) scan at screening. History of radiation pneumonitis in the radiation field (fibrosis) is allowed

- History of symptomatic deep vein thrombosis or pulmonary embolism within 6 months of enrollment
- Any medical condition likely to interfere with assessment of safety or efficacy of study treatment
- History of severe immediate hypersensitivity reaction to tocilizumab or any of the agents used in this study
- Treatment with a live, attenuated vaccine within 6 weeks prior to initiation of study treatment or anticipation of need for such a vaccine during the course of the study
- Women of childbearing potential who were pregnant or breastfeeding because of the potentially dangerous effects of chemotherapy on the fetus or infant. Patients of either sex who were not willing to practice birth control from the time of consent and at least 6 months after the last dose of axi-cel or SOC chemotherapy
- In the investigator's judgment, the patient was unlikely to complete all protocol-required study visits or procedures, including follow-up visits, or comply with the study requirements for participation

Per the original protocol, the timeframe for relapsed disease of CR to first-line therapy followed by biopsy-proven disease relapse was ≤12 months of initiating first-line therapy. After an amendment on March 19, 2019, this was broadened to ≤12 months of first-line therapy (either from initiation or completion of first-line therapy).

Randomization

Patients were randomized using the Interactive Voice/Web Response System (IXRS). To randomize patients, an authorized site representative logged into the IXRS to generate a randomization number. The randomization was accomplished by entering pertinent information detailed in the IXRS user manual. After data were entered, a single, unique randomization number and randomization treatment for each patient were assigned, and patients were enrolled and randomized into the study. There were no restrictions to randomization.

Per the original protocol, randomization was stratified by relapse ≤6 months of initiating first-line therapy and relapse >6 and ≤12 months of initiating first-line therapy. This was broadened to relapse ≤6 months of first-line therapy (either from initiation or completion of first-

line therapy) and relapse >6 and ≤12 months of first-line therapy (either from initiation or completion of first-line therapy) in a protocol amendment on March 19, 2019. Randomization was stratified by response to first-line therapy (primary refractory, vs. relapse ≤6 months of first-line therapy, vs. relapse >6 and ≤12 months of first-line therapy) and second-line age-adjusted IPI (sAAIPI; 0-1 vs. 2-3) as assessed at screening. Patients initiated either leukapheresis (for axi-cel cohort) or SOC therapy (for SOC cohort) within approximately 5 days of randomization.

Bridging therapy

Bridging therapy was limited to corticosteroids, such as dexamethasone at a dose of 20-40 mg or equivalent, either by mouth or IV daily for 1-4 days, at the investigator's discretion for patients with high disease burden at screening, administered after leukapheresis, and completed ≥5 days before axi-cel. Choice of corticosteroid and dosing was adjusted for age/comorbidities or per clinical judgment.

Platinum-based chemoimmunotherapy regimens used for SOC cohort

Common regimens included rituximab + gemcitabine, dexamethasone, and cisplatin/carboplatin (R-GDP), rituximab + dexamethasone, high-dose cytarabine and cisplatin (R-DHAP), rituximab + ifosfamide, carboplatin, and etoposide (R-ICE), and rituximab + etoposide, methylprednisolone, cytarabine, cisplatin (R-ESHAP). Because no single salvage regimen has demonstrated superiority,[2,3] institutional preference and toxicity profile were considered when selecting SOC regimen for patients. Suggested dosing of common regimens is shown below.

SOC chemotherapy	Dosing
R-GDP	• Rituximab 375 mg/m^2 day 1 (or day 8) • Gemcitabine 1 g/m^2 on days 1 and 8 • Dexamethasone 40 mg on days 1-4 • Cisplatin 75 mg/m^2 on day 1 (or carboplatin AUC=5)
R-DHAP	• Rituximab 375 mg/m^2 before chemotherapy • Dexamethasone 40 mg/day on days 1-4 • High-dose cytarabine 2 g/m^2 every 12 hours for two doses on day 2 following platinum

	• Cisplatin 100 mg/m^2 24h-CI on day 1 (or oxaliplatin 100 mg/m^2)[4]
R-ICE	• Rituximab 375 mg/m^2 before chemotherapy • Ifosfamide 5 g/m^2 24h-CI on day 2 with mesna • Carboplatin AUC=5 on day 2, maximum dose 800 mg • Etoposide 100 mg/m^2/d on days 1-3
R-ESHAP	• Rituximab 375 mg/m^2 day 1 • Etoposide 40 mg/m^2/d IV on days 1-4 • Methylprednisolone 500 mg/d IV on days 1-4 or 5 • Cisplatin at 25 mg/m^2/d CI days 1-4 • Cytarabine 2 g/m^2 on day 5

24h-CI, 24-hour continuous infusion; AUC, area under the curve; CI, continuous infusion; IV, intravenous; R-GDP, rituximab + gemcitabine, dexamethasone, and cisplatin/carboplatin; R-DHAP, rituximab + dexamethasone, high-dose cytarabine and cisplatin; R-ICE, rituximab + ifosfamide, carboplatin, and etoposide; R-ESHAP, rituximab + etoposide, methylprednisolone, cytarabine, cisplatin.

Toxicity management

Due to risks associated with axi-cel treatment, infusion was delayed, and an appropriate assessment performed if a patient had any of the following conditions:

- Unresolved serious adverse reactions (especially pulmonary reactions, cardiac reactions, or hypotension), including those from previous chemotherapies
- Active uncontrolled infection
- Active graft-versus-host disease

Cytokine release syndrome (CRS) management in anti-CD19 CAR T-cell therapy was intended to prevent life-threatening conditions while preserving the benefits of antitumor effects. Patients were monitored for signs and symptoms of CRS. Diagnosis of CRS required excluding alternate causes of systemic inflammatory response, particularly infection. Patients who experienced grade ≥2 CRS were monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, an echocardiograph was considered to assess cardiac function. For severe or life-threatening CRS, intensive care supportive therapy was

considered. The table below outlines the recommended management of CRS associated with treatment with axi-cel.

CRS Grade*	Supportive Care	Tocilizumab	Corticosteroids	Follow-up
Grade 1				
Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise)	Supportive care per institutional SOC Closely monitor neurologic status	N/A	N/A	<u>Not improving after 24 hours</u> Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg)
Grade 2				
Symptoms require and respond to moderate intervention Oxygen requirement <40% FiO_2 or hypotension responsive to fluids or low dose of one vasopressor or grade 2 organ toxicity	Continuous cardiac telemetry and pulse oximetry as indicated IV fluids bolus for hypotension with 0.5 to 1.0 liter isotonic fluids Vasopressor support for hypotension not responsive to IV fluids Supplemental oxygen as indicated	Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg) Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen; maximum of three doses/24 hours. Maximum total of four doses if no clinical improvement in the signs and symptoms of CRS	If no improvement within 24 hours after starting tocilizumab, manage per grade 3	<u>Improving</u> Manage as above If corticosteroids were started: continue corticosteroids use until the event is grade 1 or less, then taper over 3 days <u>Not improving</u> Manage as grade 3 (below)

Grade 3				
Symptoms require and respond to aggressive intervention Oxygen requirement ≥ 40% FiO_2 or hypotension requiring high-dose or multiple vasopressors or grade 3 organ toxicity or grade 4 transaminitis	Management in monitored care or intensive care unit	Per grade 2	Methylprednisolone 1 mg/kg IV BID or equivalent dexamethasone (e.g., 10 mg IV every 6 hours)	<u>Improving</u> Manage as grade 2 (above) Continue corticosteroid use until the event is Grade 1 or less, then taper over 3 days <u>Not improving</u> Manage as Grade 4 (below)
Grade 4				
Life-threatening symptoms Requirements for ventilator support or continuous veno-venous hemodialysis (CVVHD) Grade 4 organ toxicity (excluding transaminitis)	Per grade 3 Mechanical ventilation and/or renal replacement therapy may be required	Per grade 2	High-dose corticosteroids: methylprednisolone 1000 mg/day IV x 3 days	<u>Improving</u> Manage as above Continue corticosteroids use until the event is grade 1 or less, then taper over 3 days <u>Not improving</u> Consider alternate immunosuppressants Contact Medical Monitor

BID, twice daily; IV, intravenous; CRS, cytokine release syndrome; CVVHD, continuous veno-venous hemodialysis; FiO_2, fraction of inspired oxygen; N/A, not applicable; SOC, standard of care. *Modified Lee et al 2014.[5]

Patients were carefully monitored for signs and symptoms of neurologic events. Patients who experienced grade ≥2 neurologic events had brain imaging, a lumbar puncture (with opening pressure assessment), regular neurologic exams, and were monitored with continuous cardiac telemetry and pulse oximetry. Transfer to intensive care was considered for potentially severe or life-threatening neurologic events. Non-sedating, anti-seizure medicines (e.g., levetiracetam) for prophylaxis against seizures were considered for grade ≥2 neurologic events

in the absence of contraindications. Tapering for levetiracetam was only done when the neurologic event was grade ≤1. Endotracheal intubation may have been required for airway protection in severe cases. In some cases, multiple anti-epileptic medications may have been needed to control seizures. Medications with sedative properties were avoided unless required to manage seizures. Leukoencephalopathy cases were managed based on clinical symptoms and follow-up magnetic resonance imaging was recommended for monitoring. The table below outlines the recommended management of neurologic events associated with treatment with axi-cel.

Neurologic Event Grade*	Supportive Care	Concurrent CRS	No Concurrent CRS	Follow-up
Grade 1				
Examples include: Somnolence-mild drowsiness or sleepiness Confusion-mild disorientation Encephalopathy-mild limiting of ADLs Dysphasia-not impairing ability to communicate	Supportive care per institutional SOC Closely monitor neurologic status Consider prophylactic non-sedating antiseizure medication	N/A	N/A	<u>Not improving</u> Continue supportive care
Grade 2				
Examples include: Somnolence-moderate, limiting instrumental ADLs Confusion-moderate disorientation Encephalopathy-limiting instrumental ADLs	Continuous cardiac telemetry and pulse oximetry as indicated Closely monitor neurologic status with serial neuro exams to include fundoscopy and Glasgow Coma Score. Consider neurology consult.	Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg) Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen; maximum of three doses in a 24-hour period. Maximum total of four doses if no	Tocilizumab not indicated Dexamethasone at 10 mg IV every 6 hours	<u>Improving</u> Manage as above Continue dexamethasone use until the event is grade 1 or less, then taper over 3 days <u>Not improving</u> Manage as grade 3 (below)

Dysphasia-moderate impairing ability to communicate spontaneously Seizure(s)	Perform brain imaging (e.g., MRI), EEG, and lumbar puncture (with opening pressure) if no contraindications Consider prophylactic nonsedating, antiseizure medication	clinical improvement in the signs and symptoms of CRS • If no improvement within 24 hours after starting tocilizumab, give dexamethasone 10 mg IV every 6 hours†, if not already taking other corticosteroids. Continue dexamethasone use until the event is grade 1 or less, then taper over 3 days		
Grade 3				
Examples include: Somnolence-obtundation or stupor Confusion-severe disorientation Encephalopathy-limiting self-care ADLs Dysphasia-severe receptive or expressive characteristics, impairing ability to read, write, or communicate intelligibly	Management in monitored care or intensive care unit	Administer tocilizumab per grade 2 In addition, administer dexamethasone 10 mg IV with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is grade 1 or less, then taper over 3 days.	Dexamethasone at 10 mg IV every 6 hours. Continue dexamethasone use until the event is grade 1 or less, then taper over 3 days	<u>Improving</u> Manage as above Continue dexamethasone use until the event is grade 1 or less, then taper over 3 days <u>Not improving</u> Manage as grade 4 (below)
Grade 4				
Life-threatening consequences	Per grade 3	Administer tocilizumab per grade 2	High-dose corticosteroids: methylprednisolone‡ 1000 mg/day IV x 3	<u>Improving</u> Manage as grade 3 (above)

Urgent intervention indicated Requirement for mechanical ventilation Consider cerebral edema (refer to table below for management of suspected cerebral edema)	Mechanical ventilation may be required	In addition, administer methylprednisolone 1000 mg IV per day with first dose of tocilizumab and continue methylprednisolone 1000 mg intravenously per day for two more days; if improves, then manage as above	days; if it improves, then manage as above.	Continue methylprednisolone use until the event is grade 1 or less, then taper over 3 days <u>Not improving</u> Consider alternate immunosuppressants Contact Medical Monitor

*Severity was graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events. †Or equivalent methylprednisolone dose (1 mg/kg). ‡Equivalent dose of dexamethasone is 188 mg/day. ADL, activities of daily life; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; EEG, electroencephalogram; IV, intravenous; MRI, magnetic resonance imaging; NA, not applicable; SOC, standard of care.

Cerebral edema was considered in patients with progressive neurologic symptoms at any grade of neurologic event. Diagnostics included serial neurologic exams. Guidelines for management of suspected cerebral edema are included in the table below.

Supportive Therapy	Tocilizumab	Corticosteroids	Follow-up
As above for neurologic events grade 4, to include: Intensive care unit supportive therapy Neuro-Intensivist consult If cerebral edema documented or strongly suspected, recommend neurosurgical consult Optimal head position with elevation of head of bed and straight neck positioning	Tocilizumab as above in grade 4 neurologic event management (tocilizumab should be given only if concurrent CRS)	High-dose corticosteroids: methylprednisolone 1000 mg/day x 3 days	<u>Improving:</u> Very slow corticosteroid taper recommended Serial neurologic exams as indicated Consider early neuro-rehabilitation <u>Not improving:</u> Repeat neuro-imaging as indicated Consider alternate immunosuppressants

Administration of diuretics and osmotherapy per institutional practice guidelines Early tracheal intubation with controlled mechanical mild hyperventilation and good oxygenation Maintain cerebral perfusion pressure with mild hypervolemia Avoid hypertension with use of anti-hypertensives (labetalol, nicardipine) Avoid potent vasodilators Pharmacological cerebral metabolic suppression (barbiturates, sedation, analgesia, and neuromuscular paralysis, as indicated) Maintain rigorous glycemic control			Consult Medical Monitor

CRS, cytokine release syndrome. Note: Information is based on a review of treatment for cerebral edema by Rabinstein, 2006.[6]

Cytopenias, including prolonged cytopenias, were managed with a thorough evaluation for a source of infection and administration of prophylactic broad-spectrum antibiotics per institutional practice guidelines. Granulocyte colony-stimulating factor (G-CSF) was given according to published guidelines. Fevers were treated with supportive measures and antipyretics. Euvolemia was maintained with addition of isotonic IV fluids (e.g., crystalloids) as clinically indicated and per institutional practice guidelines. Prolonged cytopenias beyond 30 days following axi-cel administration may have required clinical investigation, including bone marrow biopsy. Patients received platelets and packed red blood cells as needed for anemia and thrombocytopenia.

Patients were monitored for signs and symptoms of infection, and treatment with antibiotics for suspected or confirmed infections was recommended. Patients received prophylaxis for infection with pneumocystis pneumonia, herpes virus, and fungal infections according to National Comprehensive Cancer Network guidelines or standard institutional practice guidelines. Fevers were treated with acetaminophen and comfort measures, and corticosteroids were avoided. Patients who were neutropenic and febrile received broad-spectrum antibiotics and maintenance IV fluids were started on most patients with high fevers. G-CSF was given according to published guidelines (e.g., Infectious Disease Society of America). Patients with B-cell aplasia leading to hypogammaglobulinemia received IV immunoglobulin per institutional practice guidelines. Screening for hepatitis B virus, hepatitis C virus, and HIV was performed in accordance with clinical guidelines before collection of cells for manufacturing.

CAR T-cell levels and immunogenicity

Summary statistics were provided for anti-CD19 CAR T cells measured in blood. The presence, expansion, and persistence of CAR T cells were measured in peripheral blood mononuclear cells as previously reported.[7] Briefly, blood-derived and cryopreserved peripheral blood mononuclear cells were analyzed by quantitative PCR (qPCR) to assess the levels of anti-CD19 CAR T cells over time. qPCR values were converted into cells/µl of blood. Post-infusion peak, time to peak, area under the curve (AUC) from day 0 to day 28 (AUC_{0-28}), and the persistence of anti-CD19 CAR T cells up to 24 months in patients with evaluable samples are presented herein.

Potential immunogenicity was initially identified by the development of antibodies that tested positive for reactivity against the murine monoclonal antibody FMC63 (parent antibody for the single-chain variable region fragment [scFv] used for production of the anti-CD19 CAR in axi-cel), as measured by a traditional sandwich-based enzyme-linked immunosorbent assay (ELISA). Positive samples underwent further testing with a confirmatory flow cytometry cell-based assay to determine whether the signal observed in the initial screening assay (ELISA) was due to the antibody binding to a properly folded scFv expressed on the surface of an anti-CD19 CAR T cell.

Disease assessments

Disease assessments were evaluated per Lugano Classification Response Criteria.[8] Screening fluorodeoxyglucose (FDG)-positron emission tomography (PET) from skull base to mid-thighs and diagnostic quality contrasted-enhanced CT from skull base through lesser trochanters (PET-CT), along with appropriate imaging of all other disease sites were required to confirm eligibility and to establish baseline within 28 days prior to randomization. Patients had their first post-treatment planned PET-CT tumor assessment within the day 50 assessment period calculated from randomization date). Disease assessments were conducted at day 50, 100, and 150 from randomization. PET-CTs continued through month 9 or until change in lymphoma therapy or disease progression, whichever came first. If the patient's disease did not progress by month 9, disease assessments were evaluated per CT scans where complete response was suspected and per PET-CTs where a PR was suspected. Patients with symptoms suggestive of disease progression were evaluated for progression at the time of symptoms. PET-CT could be performed at any time disease progression was suspected. FDG-PET assessment took precedence over CT assessments for time points when both were available. If only CT was available for a time point, assessment may have been affected by the PET-CT assessment at the prior time point. In addition to investigator's assessment, PET-CT scans were submitted to and reviewed by an independent central reviewer blinded to treatment arm. A patient's bone marrow involvement was confirmed by PET-CT or bone marrow biopsy and aspirate prior to randomization.

Lugano classification response criteria[8]

5-Point Scale (5PS)[9]

Score	Description
1	No uptake above background
2	Uptake ≤mediastinum
3	Uptake >mediastinum but ≤liver
4	Uptake moderately higher than liver
5	Uptake markedly higher than liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma

PET-CT–based complete metabolic response required the following:

- A 5PS score of 1, 2, or 3 with or without a residual mass

    - In Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow, uptake may have been greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may have been inferred if uptake at sites of initial involvement was no greater than normal surrounding tissue, even if the tissue had high physiologic uptake
- No new sites of disease
- No evidence of FDG-avid disease in bone marrow

CT-based complete radiologic response required the following:

- Target nodes/nodal masses must regress to ≤1.5 cm in longest transverse diameter of lesion (LDi)
- No extralymphatic sites of disease
- Absent nonmeasured lesion
- Regression of organ enlargement to normal
- No new sites of disease
- Normal bone marrow by morphology; if indeterminate, negative by immunohistochemistry

PET-CT–based partial metabolic response required the following:

- A 5PS score of 4 or 5, with reduced uptake compared with baseline (screening), and residual mass(es) of any size
    - At interim, this suggested responding disease
    - At end of treatment, this suggested residual disease
- No new sites of disease
- Residual uptake higher than uptake in normal bone marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed)
- If there were persistent focal changes in the marrow in context of a nodal response, consideration was given for further evaluation with magnetic resonance imaging or biopsy or an interval scan

CT-based partial radiologic response required the following:

- Decrease of ≥50% in the sum of product diameters (SPD) of up to six target measurable nodes and extranodal sites

    - When a lesion was too small to measure via CT, 5 mm × 5 mm was assigned as the default value
    - When no longer visible, 0 × 0 mm
    - For a node >5 mm × 5 mm, but smaller than normal, actual measurements were used for calculation
- Nonmeasured lesions were absent/normal, regressed, but not increased
- Spleen must have regressed by >50% in length beyond normal
- No new sites of disease

PET-CT–based stable disease (no metabolic response) required the following:

- A 5PS score of 4 or 5, with no significant change in FDG uptake compared with baseline (screening) at an interim time point or end of treatment
- No new sites of disease
- No change from baseline in bone marrow

CT-based stable radiologic disease required the following:

- Decrease of <50% from baseline in the SPD of up to six dominant, measurable nodes and extranodal sites; no criteria for progressive disease were met
- No increase consistent with progression in nonmeasured lesion and organ enlargement
- No new sites of disease

PET-CT–based progressive metabolic disease required the following:

- 5PS score of 4 or 5 with an increase in intensity of uptake from nadir and/or
- New FDG-avid foci consistent with lymphoma at interim or end of treatment assessment
- New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may have been considered
- New or recurrent FDG-avid foci in bone marrow

CT-based progressive radiologic disease required at least one of the following:

- An individual node/lesion must have been abnormal with
    - LDi >1.5 cm, and

    - Increase by ≥50% from cross-product of LDi and perpendicular diameter nadir, and
    - An increase in LDi or shortest axis perpendicular to the LDi (SDi) from nadir
        - 0.5 cm for lesions ≤2 cm
        - 1.0 cm for lesions >2 cm
    - In the setting of splenomegaly, the splenic length must have increased by >50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must have increased by at least 2 cm from baseline
    - New or recurrent splenomegaly
- New or clear progression of pre-existing nonmeasured lesions
- New lesion
    - Regrowth of previously resolved lesions
    - A new node >1.5 cm in any axis
    - A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must have been unequivocal and must have been attributable to lymphoma
    - Assessable disease of any size unequivocally attributable to lymphoma
- New or recurrent bone marrow involvement

Cell of origin determination

Cell of origin per central laboratory was determined by gene expression profiling (NanoString); per investigator, cell of origin was determined based on institutional guidelines.

Statistical analysis

The hypothesis for ZUMA-7 was that axi-cel will prolong event-free survival (EFS) compared with SOC therapy in adult patients with R/R LBCL. The hypothesized treatment effect corresponded to a 50% improvement in EFS. An EFS hazard ratio (HR; axi-cel/SOC cohort) of 0.67 was hypothesized, assuming exponential distribution for EFS and a median EFS of 4 months in the SOC cohort. This implied a 50% relative improvement in EFS and corresponded to median EFS of 4 versus 6 months (SOC versus axi-cel cohort). According to the original protocol and up to a protocol amendment on March 19, 2019, the primary analysis event trigger was for 270 EFS events. After a protocol amendment on June 25, 2020, this was changed to approximately 250 events. “Approximately” was removed after a United States-specific protocol

amendment on September 16, 2020. The primary analysis was planned when 250 EFS events were observed; the study was sized to achieve at least 90% power at the 1-sided 2.5% significance to detect a 50% improvement in EFS. The minimum effect size that could be determined to be statistically significant was an EFS HR of 0.79, or a 27% relative improvement in EFS. Further, assuming a concave accrual distribution with 50% of accrual in the last 33% of the accrual period of 24 months and a 10% rate (5% by month 1 and cumulative 10% by month 8) of loss to follow-up in the axi-cel cohort and 15% rate (10% by month 1 and cumulative 15% by month 8) of loss to follow-up in the SOC cohort, it was anticipated that the event goal would be achieved if 350 patients were randomized (175/arm) and would occur approximately 31 months after the first patient was randomized.

Analysis sets:

- Efficacy analysis set: All randomized patients and was used for the primary efficacy analyses. Patients were analyzed according to the treatment first randomized regardless of treatment received
- Safety analysis set: Subset of all randomized patients who received at least one dose of axi-cel or SOC as protocol therapy. Patients were analyzed by the protocol therapy received

Subgroup analyses of EFS were examined for the following baseline covariates:

- Age at randomization (≥65, <65 years)
- Response to first-line therapy (primary refractory, relapse ≤6 months of first-line therapy vs relapse >6 and ≤12 months of first-line therapy)
- Age-adjusted IPI (0 to 1 vs 2 to 3) at time of screening
- Molecular subgroup (GBC, ABC)
- Double-hit (C-*MYC* alterations and either *BCL-2* or *BCL-6* alterations) status by FISH
- Triple-hit (*BCL-2*, *BCL-6*, and C-*MYC* alterations) status by FISH

For the primary analysis of EFS, disease progression events and censoring times were determined by blinded central review. The following criteria were used to further define censoring times:

- Patients alive, in response, and with no new therapy were censored at the last evaluable disease assessment
- Patients with no evaluable disease assessment by Day 150 assessment post-randomization were not considered to have an EFS event, and the EFS time was censored at the randomization date
- The EFS time for patients in the axi-cel cohort who underwent stem cell transplant (SCT) in the absence of any documented progression or new therapy was censored on the day of SCT
- For patients in the SOC cohort, total body irradiation, high-dose therapy, and SCT that occurred while the patient was in response from protocol-specified induction therapy were not considered an EFS event. The EFS time for SOC cohort patients alive, progression-free, and with no new lymphoma therapy was censored at the last evaluable disease assessment date

Statistical testing followed a hierarchical scheme. Outcomes for patients with R/R LBCL after first-line chemoimmunotherapy treated with SOC have been previously described.[2,3,10-12] EFS and OS assumptions in the SOC cohort were simulated based on previous studies and assumed exponential time-to-event distributions. Median EFS in the SOC cohort was assumed to have exponential distribution with median 4.0 months and median OS of 15.8 months.

Analysis of OS

An interim analysis of OS occurred at the time of the primary analysis, reported herein. The primary analysis of OS will be conducted when approximately 210 deaths are observed or no later than 5 years after the first patient was randomized.

According to the original protocol and up to a protocol amendment on March 19, 2019, a sensitivity analysis of OS was not included. After a protocol amendment on June 25, 2020, sensitivity analysis of OS was included to address the confounding effect from treatment switching and was conducted using the Rank Preserving Structural Failure Time (RPSFT) model[13] and Inverse Probability of Censoring Weights (IPCW), 2-stage Cox regression model, and other exploratory treatment switching adjustment methods.

The RPSFT model is a method used to adjust for treatment switching in trials with survival outcomes[14]:

> Treatment switching occurs when patients switch from their randomized cohort to another treatment during the study. The method is randomization based and used only the randomized treatment group, observed event times, and treatment history in order to estimate a causal treatment effect. The treatment effect, ψ, was estimated by balancing counter-factual event times (i.e., the time that would be observed if no treatment were received) between treatment groups. A g-estimation procedure was used to find the value of ψ such that a test statistic Z(ψ)=0. Recensoring was performed as censoring becomes informative on the counter-factual time scale.[14]

IPCW as a treatment effect estimation method occurred in the presence of dependent censoring used in a marginal structural model[15]:

> For treatment switching cases, patients were artificially censored at the time of switch. Weights were increased for patients who did not switch but had similar baseline characteristics compared with patients who did switch. More specifically, the weights were obtained for each patient based on the inverse probability of the patient remaining in the control treatment until time, t. Treatment effect was then estimated using weighted survival analysis methods (e.g., weighted Cox regression model or weighted Kaplan-Meier curve). The assumption of the method was “no unmeasured confounders”; all baseline covariates and all post-baseline time-dependent confounders that predict both treatment switch and outcome were included.[16]

Supplementary Results

Patients

Of the 10 patients randomized to axi-cel who did not receive axi-cel, 5 received bridging steroids. Of these 5 patients, 2 experienced disease progression or an adverse event indicative of clinical progression, and 1 experienced small intestinal perforation related to bridging per investigator assessment.

Axi-cel was successfully manufactured for all patients who underwent leukapheresis. The median time from leukapheresis to product delivery to the trial site was 18 days, and the median (Q1, Q3) time from randomization to axi-cel infusion was 29 days (27, 34). Of note, product arrival on site was dependent on when the investigator requested delivery, and infusion was dependent on patient scheduling and confirmation of eligibility for axi-cel infusion, which could be subject to unforeseen transient delays.

Subsequent stem cell therapy

Nineteen (11%) patients treated with axi-cel on protocol received subsequent SCT (third-line or later). Of these, 11 (6%) and 8 (5%) received ASCT and allogeneic SCT, respectively. A total of 10 (53%) patients died and 9 (47%) remained alive following these therapies at the time of the data cutoff.

Intensive care unit utilization

A total of 42 (25%) patients in the axi-cel cohort and 9 (5%) patients in the SOC cohort were admitted to the intensive care unit (ICU). Median duration of ICU hospitalization was 5 days (range, 1-12) and 3 days (range, 2-17 days) in the axi-cel and SOC patients, respectively. Median duration of hospitalization for axi-cel infusion was 16 days (range, 5-103); median duration of inpatient hospitalization for stem cell transplant in the SOC cohort was 21 days (range, 1-53).

EFS sensitivity analysis

An assessment of nonproportional hazards was performed and, as the proportional hazards assumption was not satisfied, a corresponding sensitivity analysis was conducted. The sensitivity analysis showed the weighted average overall hazard ratio of 0.444 (95% CI: 0.333-

0.590) with 2-sided *P* value <0.0001, which demonstrates consistency with the result from the primary analysis.

Preplanned OS sensitivity analysis

A preplanned OS sensitivity analysis was conducted to address the confounding effects of treatment switching to subsequent cellular immunotherapy in the SOC cohort, given that the survival difference may have been blunted and underestimated in traditional intent-to-treat analysis. Results showed a difference in OS in favor of axi-cel with a stratified HR of 0.580 (95% CI, 0.416-0.809; **Fig. S3A**) using the RPSFT model. The validated and commonly-used Rank Preserving Structural Failure Time (RPSFT) model preserves randomization,[13] revealing the difference in treatment effect if SOC patients did not receive subsequent cellular immunotherapy. An additional analysis was conducted using the Inverse Probability of Censoring Weights (IPCW) model, with a stratified HR of 0.695 (95% CI, 0.461-1.049; **Fig. S3B**).

Figure S1. Summary of Objective Response Rate Per Central Assessment.

Figure shows summary of best response per central assessment in axi-cel (N=180) and SOC (N=179) cohorts. Data represent n (%) of patients with response. Response rates by central assessment were largely consistent with those by investigator assessment; ORR by investigator assessment was 83% (149/180) and 45% (80/179) in the axi-cel and SOC cohorts, respectively. CR rate was 61% (110/180) and 34% (61/179) in the axi-cel and SOC cohorts, respectively, and PR rate was 22% (39/180) and 11% (19/179). *In the axi-cel cohort, response assessments were not done for four patients. In the SOC cohort, there were four patients with undefined disease and 14 who did not have response assessments done. NE, not evaluable; ORR, objective response rate; PD, progressive disease; SD, stable disease; SOC, standard of care.

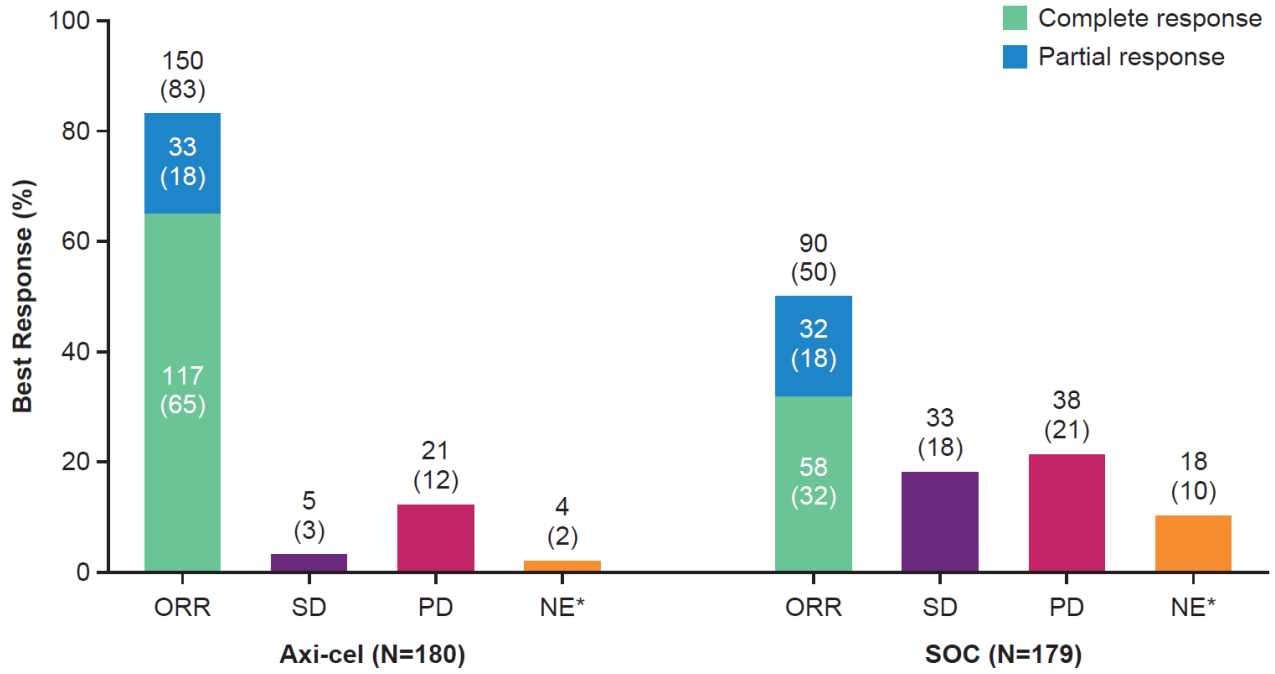


Figure S2. Objective Response Rate by Disease Subtype.

The 95% CIs were calculated with the use of the Clopper-Pearson method and are not adjusted for multiplicity and should not be used for inference. Axi-cel, axicabtagene ciloleucel; BCL2, B-cell lymphoma 2; BCL6, B-cell lymphoma 6; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HR, hazard ratio; HGBL, high-grade B-cell lymphoma; ORR, objective response rate; SOC, standard of care.

	Axi-cel ORR/N	%	SOC ORR/N	%	Odds Ratio (95% CI)
Overall	150/180	83	90/179	50	5.31 (3.08-8.90)
Disease type per central laboratory					
DLBCL	105/126	83	67/120	56	4.10 (2.13-7.80)
HGBL with or without *MYC* and *BCL2* and/or *BCL6* rearrangement	25/31	81	11/26	42	5.35 (1.21-20.45)
Disease type per investigator					
DLBCL not otherwise specified	92/110	84	57/116	49	5.58 (2.75-10.91)
Large cell transformation from FL	17/19	89	15/27	56	6.29 (0.98-62.11)
HGBL with or without *MYC* and *BCL2* and/or *BCL6* rearrangement	36/43	84	12/27	44	5.80 (1.59-20.13)

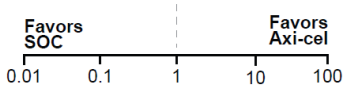
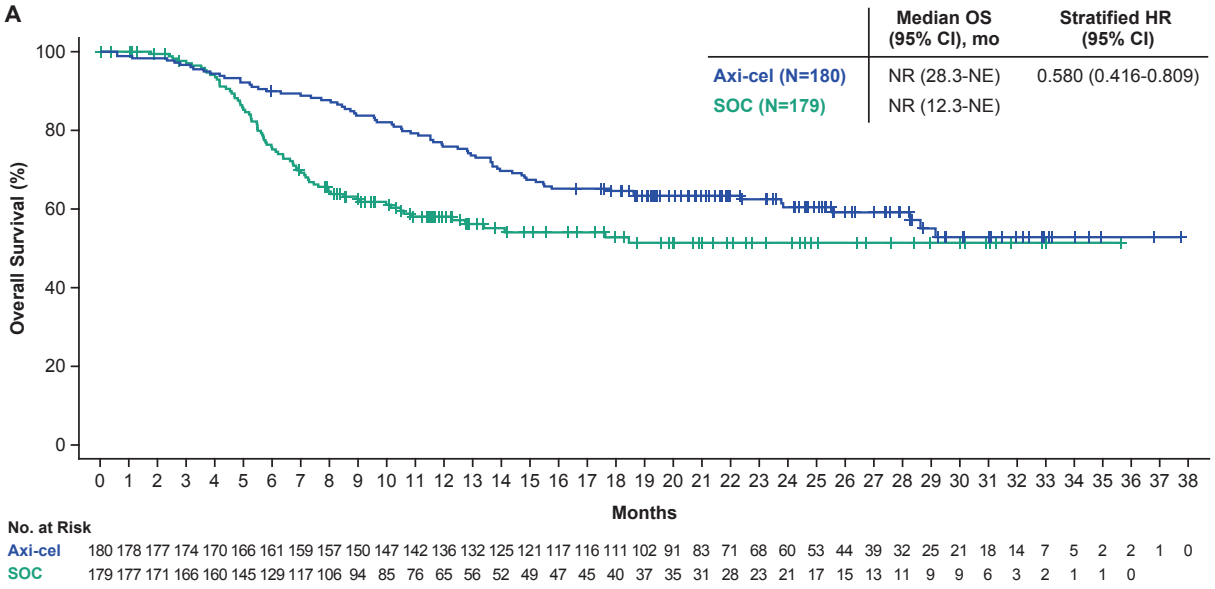


Figure S3. Overall Survival Treatment Switching Sensitivity Analysis.

Sensitivity analysis of overall survival using the Rank Preserving Structural Failure Time method was performed to address the confounding effect from treatment switching in axi-cel (N=180) and SOC (N=179) cohorts. The treatment switching rate was defined as the proportion of patients randomized to the SOC cohort who received commercially available or investigational cellular immunotherapy after non-response to or relapse after SOC. Panel A shows Kaplan-Meier estimate of overall survival with sensitivity analysis using the Rank Preserving Structural Failure Time model. Panel B shows the hazard ratio of overall survival with sensitivity analysis using a second method, the Inverse Probability of Censoring Weights model. OS outcomes in the current study are immature given that OS was only evaluated as an interim analysis at the time of the primary event-free survival analysis reported herein; additional follow-up is ongoing and not currently complete for OS. Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; HR, hazard ratio; NE, not evaluable; NR, not reached; SOC, standard of care.

A



B

Overall Survival, Inverse Probability of Censoring Weights Model	Axi-cel N=180	SOC N=179
Treatment switching from standard of care to cellular immunotherapy, n (%)	-	100 (56)
Hazard ratio (95% CI), stratified adjusting for treatment switching	0.695 (0.461-1.049)	-

Figure S4. Duration of Response Per Central Review.

Axi-cel, axicabtagene ciloleucel; CI, confidence interval; DOR, duration of response; HR, hazard ratio; NE, not estimable; SOC, standard of care.

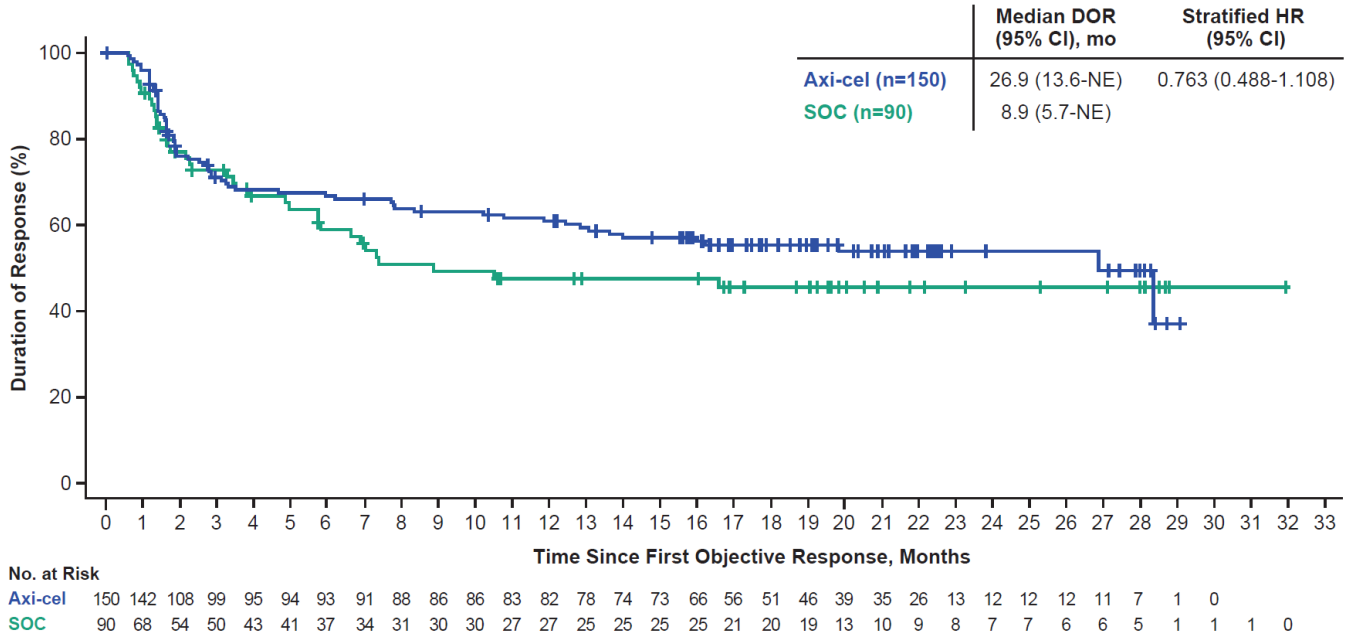


Figure S5. CAR T-Cell Expansion.

Figure shows median (Q1, Q3) number of CAR T cells in blood (cells/μL) over time, from baseline to 24 months post-infusion. CAR, chimeric antigen receptor.

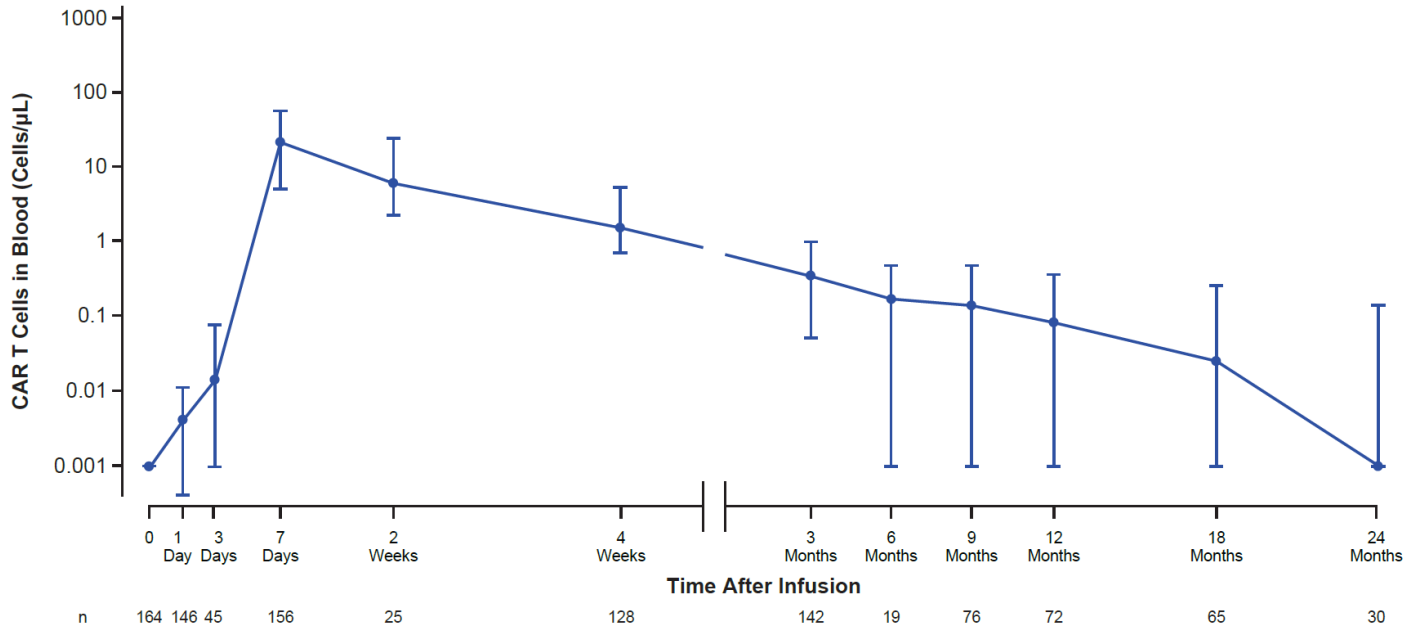


Table S1. Representativeness of the ZUMA-7 Study Participants.

Category	Key Findings
Special considerations related to	
Age	LBCL predominantly affects older adults. Irrespective of race or sex, LBCL diagnoses are made at increasing frequency with increasing age. The patient population seeking second-line treatment observed in real-world evidence is, on average, older than those participating in clinical trials.
Race or ethnic group	The majority of patients with LBCL treated in the second line are non-Hispanic whites. This is aligned with the observation that most patients diagnosed with LBCL are non-Hispanic whites, followed by a smaller proportion of other race or ethnic groups.
Sex and gender	Overall, LBCL proportionately affects more men than women. This prevalence is exaggerated in the second-line clinical trials assessed compared with that observed in real-world evidence. Generally, slightly more men than women are diagnosed with LBCL, though this varies across race and ethnic groups.
Overall representativeness of this trial	The demographics of the participants in the ZUMA-7 study were consistent with those expected of this relapsed/refractory patient population with LBCL treated in clinical trials. The median patient age, the ratio of men to women, and the proportion of non-Hispanic white patients was consistent with that observed in clinical trials in this setting. However, a greater proportion of patients aged ≥65 years were enrolled in ZUMA-7 compared with most of the clinical studies analyzed. Generally, the patient demographics in ZUMA-7, along with the clinical studies analyzed here, demonstrate the underrepresentation of racial minorities in cancer trials. For example, a greater proportion of non-Hispanic whites were enrolled and treated in ZUMA-7 compared with other racial and ethnic groups versus what may be expected based on real-world evidence. Additional inclusive research is needed to address known inequalities in medical practice and complete datasets that include full patient demographic information.

To generate this table, the PubMed database was searched to identify clinical trials in humans published in English from 2010 to November 19, 2021, using the terms “large b-cell lymphoma” AND “salvage”

AND “relapse OR refractory”, resulting in 76 hits. To find the most comparable patient population to that of ZUMA-7, hits were further refined to focus on Phase 3, second-line studies in adults who were intended for transplant and where at least one of the study arms was a standard-of-care regimen. The final number of results from this search was 3. Given that all characteristics of patient demographics were not reported in the most relevant studies, an additional search was performed to capture patients within real-world evidence reporting. For this, the terms “large B-cell lymphoma” AND “real world” AND “relapsed OR refractory” AND “transplant” were used, resulting in 29 hits. These hits were further refined by selecting for those reporting demographics of adult patients who were transplant intended after first-line therapy. The final number of results from this search was 3, with an overall total of 6 clinical trial and real-world evidence publications found. Though the search parameters did not specify studies within the United States, it should be noted that 5 of the 6 identified publications that met the aforementioned criteria were conducted within the United States and therefore may not be representative of global findings. Given the limited number of relevant publications, the authors also considered data from the United States-specific SEER database, including a publication by Vaughn et al. that utilized the database, to uncover any differences among patients with LBCL at time of diagnosis.

These considerations were generated based on the collective reporting from: Gisselbrecht C, et al. J Clin Oncol 2010;28:4184-90; Crump M, et al. J Clin Oncol 2014;32:3490-6; van Imhoff GW, et al. J Clin Oncol 2017;35:544-51; Chien HC, et al. Future Oncol 2021;17:411-22; Fuji S, et al. Ann Hematol 2021;100:2253-60; Kilgore KM, et al. Future Oncol 2021;ePub; Vaughn JL, et al. *Cancer Med.* 2021;10:7330-7338; and the SEER database.

LBCL, large B-cell lymphoma; SEER, Surveillance, Epidemiology, and End Results.

Table S2. Baseline Characteristics of SOC Patients Who Proceeded to ASCT.

Characteristic	SOC n=62
ECOG PS of 1, n (%)	20 (32)
Disease stage, n (%)	
I-II	11 (18)
III-IV	51 (82)
sAAIPI of 2-3, n (%)*	23 (37)
Molecular subgroup per central laboratory, n (%)	
Germinal center B-cell like	39 (63)
Activated B-cell like	3 (5)
Unclassified	2 (3)
Not applicable	7 (11)
Missing	11 (18)
Response to 1L at randomization, n (%)†	
Primary refractory	38 (61)
Relapse ≤12 months of initiation or completion of 1L therapy	24 (39)
Disease type per central laboratory, n (%)	
DLBCL‡	47 (76)
HGBL, NOS	1 (2)
HGBL, with *MYC/BCL2/BCL6* rearrangement	8 (13)
Not confirmed/missing	3 (5)
Other	3 (5)

Disease type per investigator, n (%)	
LBCL not otherwise specified	36 (58)
T cell/histiocyte rich LBCL	5 (8)
Large cell transformation from follicular lymphoma	11 (18)
HGBL with or without *MYC* and *BCL2* and/or *BCL6* rearrangement	10 (16)
Prognostic marker per central laboratory, n (%)	
HGBL – double/triple-hit	8 (13)
Double expressor lymphoma	28 (45)
MYC rearrangement	1 (2)
N/A	23 (37)
Missing	2 (3)
Positive CD19 status by IHC per central laboratory, n (%)[§]	50 (81)
Elevated LDH (LDH>ULN per local laboratory reference range), n (%)	27 (44)
Bone marrow involvement[‖], n (%)	6 (10)

*Per sAAIPI at randomization, which was similar to sAAIPI per investigator as entered into the clinical database. [†]Per response to first-line therapy at randomization. [‡]Definition of DLBCL per central laboratory included cases of incomplete evaluation due to inadequate sample amount or sample type, for which further classification of DLBCL subtype was not possible. DLBCL NOS, per World Health Organization 2016 definition[1], is also included. [§]CD19 staining was not required for participation in the study. [‖]As collected on the diagnosis history case report form.
1L, first-line; ASCT, autologous stem cell transplant; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; HGBL, high grade B-cell lymphoma; IHC, immunohistochemistry; LBCL, large B-cell lymphoma; LDH, lactate dehydrogenase; NOS, not otherwise specified; sAAIPI, second-line age-adjusted International Prognostic Index; SOC, standard of care; ULN, upper limit of normal.

Table S3. SOC Chemotherapy Regimens and Responses Among Patients Who Received HDT-ASCT.

n (%)	SOC N=168
Patients who received any standard-of-care second-line salvage chemotherapy*	168 (100)
Patients who responded with CR/PR	80 (48)
Patients who responded with CR/PR and received HDT-ASCT†	64 (38)
R-ICE	84 (50)
Patients who responded with CR/PR	42 (25)
Patients who responded with CR/PR and received HDT-ASCT	35 (21)
R-ESHAP	5 (3)
Patients who responded with CR/PR	4 (2)
Patients who responded with CR/PR and received HDT-ASCT	2 (1)
R-GDP	42 (25)
Patients who responded with CR/PR	21 (13)
Patients who responded with CR/PR and received HDT-ASCT	15 (9)
R-DHAP/R-DHAX	37 (22)
Patients who responded with CR/PR	13 (8)
Patients who responded with CR/PR and received HDT-ASCT	10 (6)

*The median number of cycles of salvage therapy in the SOC cohort was 2. †Of the 64 patients who reached HDT-ASCT, per investigator assessment, 18 (28%) patients and 46 (72%) patients had a best overall response prior to ASCT of PR and CR, respectively. CR, complete response; HDT-ASCT, high-dose therapy with autologous stem cell transplant; PR, partial response; R-DHAP/R-DHAX, rituximab + dexamethasone, high-dose cytarabine, and cisplatin/oxaliplatin; R-ESHAP, rituximab + etoposide, methylprednisolone, cytarabine, and cisplatin; R-GDP, rituximab + gemcitabine, dexamethasone, and cisplatin/carboplatin; R-ICE, rituximab + ifosfamide, carboplatin, and etoposide; SOC, standard of care.

Table S4. Kaplan-Meier Estimates of Event-Free Survival in Axi-cel and SOC Cohorts.

% (95% CI)	Axi-cel N=180	SOC N=179
3-month EFS	80.6 (74.0-85.6)	40.5 (33.2-47.8)
6-month EFS	51.1 (43.6-58.1)	26.6 (20.2-33.3)
9-month EFS	49.4 (42.0-56.5)	19.4 (13.8-25.6)
12-month EFS	47.2 (39.8-54.3)	17.6 (12.3-23.6)
15-month EFS	43.9 (36.5-50.9)	17.0 (11.8-23.0)
18-month EFS	41.5 (34.2-48.6)	17.0 (11.8-23.0)
21-month EFS	41.5 (34.2-48.6)	16.3 (11.1-22.2)
24-month EFS	40.5 (33.2-47.7)	16.3 (11.1-22.2)
27-month EFS	40.5 (33.2-47.7)	16.3 (11.1-22.2)

Event-free survival was assessed by blinded central review. Axi-cel, axicabtagene ciloleucel; EFS, event-free survival; SOC, standard of care.

Table S5. Serious Adverse Events Occurring in at Least Three Patients in the Overall Population.

	Axi-cel N=170		SOC N=168	
n (%)	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Any serious adverse event	85 (50)	72 (42)	77 (46)	67 (40)
Pyrexia	27 (16)	1 (1)	8 (5)	0 (0)
Encephalopathy	17 (10)	15 (9)	1 (1)	0 (0)
Hypotension	15 (9)	7 (4)	3 (2)	3 (2)
Pneumonia	8 (5)	6 (4)	4 (2)	3 (2)
Aphasia	9 (5)	8 (5)	0 (0)	0 (0)
B-cell lymphoma	7 (4)	7 (4)	5 (3)	5 (3)
Confusional state	6 (4)	4 (2)	0 (0)	0 (0)
Neutropenia*	6 (4)	5 (3)	4 (2)	4 (2)
Somnolence	5 (3)	3 (2)	0 (0)	0 (0)
Tremor	5 (3)	1 (1)	0 (0)	0 (0)
Acute kidney injury	3 (2)	2 (1)	8 (5)	4 (2)
Atrial fibrillation	4 (2)	3 (2)	2 (1)	0 (0)
Febrile neutropenia	4 (2)	4 (2)	22 (13)	22 (13)
Abdominal pain	3 (2)	2 (1)	2 (1)	1 (1)
Hypoxia	3 (2)	1 (1)	2 (1)	2 (1)
Dyspnea	3 (2)	3 (2)	1 (1)	1 (1)
Headache	4 (2)	3 (2)	0 (0)	0 (0)
Fatigue	3 (2)	2 (1)	0 (0)	0 (0)

COVID-19	3 (2)	3 (2)	0 (0)	0 (0)
Muscular weakness	3 (2)	2 (1)	0 (0)	0 (0)
Anemia	1 (1)	1 (1)	3 (2)	3 (2)
Decreased appetite	1 (1)	1 (1)	3 (2)	3 (2)
Hyponatremia	2 (1)	2 (1)	1 (1)	1 (1)
Malaise	2 (1)	0 (0)	1 (1)	0 (0)
Sinus tachycardia	2 (1)	1 (1)	2 (1)	1 (1)
Syncope	1 (1)	1 (1)	3 (2)	3 (2)
Back pain	1 (1)	0 (0)	2 (1)	2 (1)
Sepsis	2 (1)	2 (1)	4 (2)	4 (2)
Nausea	1 (1)	0 (0)	2 (1)	2 (1)
Dehydration	0 (0)	0 (0)	3 (2)	3 (2)
Thrombocytopenia[†]	0 (0)	0 (0)	6 (4)	6 (4)

*Combined Medical Dictionary for Regulatory Activities preferred terms of neutropenia and neutrophil count decreased. [†]Combined Medical Dictionary for Regulatory Activities preferred terms of thrombocytopenia and platelet count decreased. Axi-cel, axicabtagene ciloleucel; SOC, standard of care.

Table S6. Summary of Cytopenias Present on or After 30 Days From Initiation of Definitive Therapy on Protocol*.

	Axi-cel N=170		SOC Patients who Proceeded to ASCT n=62	
n (%)	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Any prolonged cytopenia	70 (41)	49 (29)	22 (35)	12 (19)
Prolonged thrombocytopenia†	32 (19)	11 (6)	15 (24)	8 (13)
Platelet count decreased	17 (10)	5 (3)	8 (13)	3 (5)
Thrombocytopenia	16 (9)	6 (4)	7 (11)	5 (8)
Prolonged neutropenia‡	56 (33)	44 (26)	6 (10)	3 (5)
Neutrophil count decreased	26 (15)	20 (12)	2 (3)	0 (0)
Neutropenia	29 (17)	22 (13)	4 (6)	3 (5)
Febrile neutropenia	4 (2)	4 (2)	0 (0)	0 (0)
Prolonged anemia§	23 (14)	5 (3)	14 (23)	6 (10)
Anemia	22 (13)	5 (3)	14 (23)‖	6 (10)
Anemia macrocytic	1 (1)	0 (0)	0 (0)	0 (0)
Hematocrit decreased	1 (1)	0 (0)	0 (0)	0 (0)

*30 days from receipt of axi-cel infusion or the first dose of high-dose therapy.

†Thrombocytopenia was identified with SMQ hematopoietic thrombocytopenia (narrow).

‡Neutropenia was identified using the MedDRA preferred terms of neutropenia, neutrophil count decreased, and febrile neutropenia. §Anemia was identified using the SMQ hematopoietic erythropenia (broad). ‖One patient was excluded as anemia was present prior to definitive therapy.

Multiple instances of the same adverse event in one patient are counted once at the worst grade for each patient. Adverse events started on or after high-dose therapy were included. Adverse events were coded using MedDRA version 23.1 and graded per Common Terminology

Criteria for Adverse Events version 4.03. ASCT, autologous stem cell transplant; axi-cel, axicabtagene ciloleucel; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, Standardized MedDRA Queries; SOC, standard of care.

Table S7. Treatment-emergent Hypogammaglobulinemia by Worst Grade.

n (%)	Axi-cel N=170	SOC N=168	Overall N=338
All	19 (11)	1 (1)	20 (6)
Grade 1	6 (4)	1 (1)	7 (2)
Grade 2	13 (8)	0 (0)	13 (4)

Axi-cel, axicabtagene ciloleucel; SOC, standard of care.

Table S8. Summary of B-cell Aplasia by Baseline Status.

	Axi-cel **N=160**
Overall, n	160
No B cells up to 3 months postinfusion, n (%)	76 (48)
No B cells up to 6 months postinfusion, n (%)	75 (47)
No B cells up to 9 months postinfusion, n (%)	61 (38)
No B cells up to 12 months postinfusion, n (%)	57 (36)
No B cells up to 18 months postinfusion, n (%)	55 (34)
No B cells at baseline, n	60 (38)
No B cells up to 3 months postinfusion, n (%)	37 (23)
No B cells up to 6 months postinfusion, n (%)	36 (23)
No B cells up to 9 months postinfusion, n (%)	31 (19)
No B cells up to 12 months postinfusion, n (%)	30 (19)
No B cells up to 18 months postinfusion, n (%)	28 (18)
With B cells at baseline, n	81 (51)
No B cells up to 3 months postinfusion, n (%)	31 (19)
No B cells up to 6 months postinfusion, n (%)	31 (19)
No B cells up to 9 months postinfusion, n (%)	24 (15)
No B cells up to 12 months postinfusion, n (%)	22 (14)
No B cells up to 18 months postinfusion, n (%)	22 (14)

Percentages are based on all patients who were tested. Axi-cel, axicabtagene ciloleucel

Table S9. Deaths in Axi-cel and SOC Cohorts (Safety Analysis Set).

Reason for death, n	Axi-cel n=64	SOC n=78
Progressive disease	47	64
Fatal adverse event	7	2
COVID-19	2	0
Lung adenocarcinoma	1	0
Myocardial infarction	1	0
Progressive multifocal leukoencephalopathy	1	0
Sepsis	1	0
Hepatitis B reactivation	1*	0
Cardiac arrest	0	1†
Acute respiratory distress syndrome	0	1†
Other reason for death	10	12
COVID-19	2	2
Stroke	1	0
Ischemic colitis	1	0
Progression from prior subdural hematoma	1	0
Respiratory failure	1	0
Euthanasia due to progressive disease	1	0
Pulmonary infection	1	0
Unexplained/unknown	1	3
Septic shock	1	1
Cardiopulmonary arrest	0	1

Cryptogenic organizing pneumonia	0	1
Sepsis	0	2
Urosepsis	0	1
Hyperinflammation	0	1

*Axi-cel–related fatal adverse event; †HDT-related fatal adverse event.

Fatal adverse events are those that occurred during the protocol-specified adverse event reporting period. Axi-cel, axicabtagene ciloleucel; HDT, high-dose therapy; SOC, standard of care.

Table S10. CAR T-Cell Levels.

CAR T-Cell Levels (cells/μL)	Axi-cel N=170
Baseline, median (Q1, Q3)	0 (0, 0)
Treatment day 1, median (Q1, Q3)	4.06×10^{-3} (4.12×10^{-4}, 0.01)
Treatment day 3, median (Q1, Q3)	0.01 (0.00, 0.08)
Treatment day 7, median (Q1, Q3)	21.37 (5.16, 57.04)
2 weeks post-treatment, median (Q1, Q3)	6.28 (2.31, 24.10)
4 weeks post-treatment, median (Q1, Q3)	1.57 (0.72, 5.40)
3 months post-treatment, median (Q1, Q3)	0.35 (0.05, 1.02)
6 months post-treatment, median (Q1, Q3)	0.17 (0.00, 0.47)
9 months post-treatment, median (Q1, Q3)	0.14 (0.00, 0.49)
12 months post-treatment, median (Q1, Q3)	0.08 (0.00, 0.37)
18 months post-treatment, median (Q1, Q3)	0.03 (0.00, 0.27)
24 months post-treatment, median (Q1, Q3)	0.00 (0.00, 0.14)
Peak, median (range)	25.84 (0.04-1173)
AUC_{0-28}, cells/μl×days, median (range)	236.23 (0.00-1.65×10^{4})
Time to peak, days, median (range)	8* (2-233)

*Day 8 equals 7 days after the day of axi-cel infusion (axi-cel infusion day is day 1 for the purpose of calculating time to peak). Axi-cel, axicabtagene ciloleucel; AUC_{0-28}; area under the curve from days 0 to 28; CAR, chimeric antigen receptor.

Table S11. Comparison of Axicabtagene Ciloleucel with SOC per ZUMA-7 and Published Studies

		LY.12[2,17] N=619 (ITT)		CORAL[10] N=396 (ITT); 388 (treated)			ORCHARRD[12] N=447 (randomized); N=445 (treated)		
	ZUMA-7 N=359	(R*-)DHAP N=309 (ITT)	(R*-)GDP N=310 (ITT)	R-ICE N=202 (ITT)† N=197 (treated)‡	R-DHAP N=194 (ITT)† N = 191 (treated)‡	Overall N=396 (ITT)† N=388 (treated)‡	R-DHAP N=223 (treated)	O-DHAP N=222 (treated)	Overall N=445 (treated)
Demographics and Baseline Characteristics									
Median age	59	55	55	54	55	55	56	58	57
Age ≥65	30%	28.8% (>60 y)	29.4% (>60 y)	0 > 65	0 > 65	0	16%	18%	17%
sAAIPI:									
• 0-1	• 54%	• 0-1: 38%	• 0-1: 38%	• 58.9%	• 55.2%	• 57.1%	• 60%	• 59%	• 59%
• 2-3	• 46%	• 2: 29%	• 2: 29%	• 37.1%	• 38.1%	• 37.6%	• 39%	• 40%	• 40%
		• ≥3: 32%	• ≥3: 33%						
R/r <12 mo of 1L therapy	100%	72%	72%	44% (r <12 mo of diagnosis)	45% (r <12 mo of diagnosis)	44% (r <12 mo of diagnosis)	70%	71%	71%
r >12 mo of 1L therapy	0%	27%	27%	55% (r ≥12 mo of diagnosis)	53% (r ≥12 mo of diagnosis)	54% (r ≥12 mo of diagnosis)	30%	28%	29%
Rituximab as 1L therapy	100%	67%	67%	60%	63%	62%	100% (88% ≥6 cycles)	100% (88% ≥6 cycles)	100% (88% ≥6 cycles)
Efficacy Results									

		LY.12[2,17] N=619 (ITT)		CORAL[10] N=396 (ITT); 388 (treated)			ORCHARRD[12] N=447 (randomized); N=445 (treated)		
	ZUMA-7 N=359	(R*-)DHAP N=309 (ITT)	(R*-)GDP N=310 (ITT)	R-ICE N=202 (ITT)† N=197 (treated)‡	R-DHAP N=194 (ITT)† N = 191 (treated)‡	Overall N=396 (ITT)† N=388 (treated)‡	R-DHAP N=223 (treated)	O-DHAP N=222 (treated)	Overall N=445 (treated)
Median FU	25 mo	53 mo		27 mo			10.9 mo		
EFS	2-y EFS Overall: • Axi: 40.5% • SOC 16.3% r ≤12 mo: • Axi: 52.6% • SOC: 17.5%	• 2-y EFS from ASCT: ~58%§ • 4-y EFS: 26% • 4-y EFS from ASCT: 48%	• 2-yr EFS from ASCT: ~50%§ • 4-yr EFS: 26% • 4-yr EFS from ASCT: 43%	3-y EFS: 26%	3-y EFS: 35%	2-y EFS§: • R/r <12 mo and prior rituximab: ~16%§ • r >12 mo and prior rituximab: ~47%§ 3-y EFS: • Overall: 31% • R/r <12 mo: 20% • r ≥12 mo: 45% • Prior rituximab: 21%	2-y EFS: 18%	2-y EFS: 16%	–
ORR	• Axi: 83% • SOC: 50%	After 2 cycles: 44% • R/r <12 m: 32% • r ≥12 m: 76%	After 2 cycles: 45% • R/r < 12 m: 38% • r ≥12 m: 63%	After salvage chemo: 63%	After salvage chemo: 63%	After salvage chemo: • Overall: 63% • R/r <12 mo: 46% • r ≥12 mo: 88% • Prior rituximab: 51%	• After salvage chemo: 42% • 3 mo after HDT/ASCT: 69%	• After salvage chemo: 38% • 3 mo after HDT/ASCT: 72%	• R/r ≤12 mo: 29% • r >12 mo: 67%

		LY.12[2,17] N=619 (ITT)		CORAL[10] N=396 (ITT); 388 (treated)			ORCHARRD[12] N=447 (randomized); N=445 (treated)		
	ZUMA-7 N=359	(R*-)DHAP N=309 (ITT)	(R*-)GDP N=310 (ITT)	R-ICE N=202 (ITT)† N=197 (treated)‡	R-DHAP N=194 (ITT)† N = 191 (treated)‡	Overall N=396 (ITT)† N=388 (treated)‡	R-DHAP N=223 (treated)	O-DHAP N=222 (treated)	Overall N=445 (treated)
		• Prior rituximab: 37%	• Prior rituximab: 44%			3 mo after ASCT: 86%			
CR	• Axi: 65% • SOC: 32%	After 2 cycles: 14% (CR/CRu)	After 2 cycles: 14% (CR/CRu)	After salvage chemo: 37%	After salvage chemo: 39%	• After salvage chemo: 38% (CR/CRu) • 3 m after ASCT: 73% (CR/CRu)	• After salvage chemo: 22% • 3 mo after HDT/ASCT: 53%	• After salvage chemo: 15% • 3 mo after HDT/ASCT: 58%	–
OS	2-y OS • Axi: 60.7% • SOC: 52.1%	• 2-y OS: ~46%§ • 2-y OS from ASCT: ~72%§ • 4-y OS: 39% • 4-y OS from ASCT: 63%	• 2-y OS: ~46%§ • 2-y OS from ASCT: ~66%§ • 4-y OS: 39% • 4-y OS from ASCT: 62%	2-y OS: ~56%§ 3-y OS: 47%	2-y OS: ~57%§ 3-y OS: 51%	3-y OS: • Overall: 50% • R/r <12 mo: 39% • r ≥12 mo: 64% • Prior rituximab: 40%	2-y OS: • Overall: 38% • Underwent ASCT: 68%	2-y OS: • Overall: 41% • Underwent ASCT: 76%	2-y OS: R/r ≤12 mo: ~31%§ r >12 mo: ~61%§
OS time (median)	• Axi: not reached • SOC: 35.1 mo	–	–	–	–	–	13.2 mo	13.9 mo	–

		LY.12[2,17] N=619 (ITT)		CORAL[10] N=396 (ITT); 388 (treated)			ORCHARRD[12] N=447 (randomized); N=445 (treated)		
	ZUMA-7 N=359	(R*-)DHAP N=309 (ITT)	(R*-)GDP N=310 (ITT)	R-ICE N=202 (ITT)† N=197 (treated)‡	R-DHAP N=194 (ITT)† N = 191 (treated)‡	Overall N=396 (ITT)† N=388 (treated)‡	R-DHAP N=223 (treated)	O-DHAP N=222 (treated)	Overall N=445 (treated)
Received Definitive Therapy									
Axi	94%	NA	NA	NA	NA	NA	NA	NA	NA
ASCT	36%‖	48%	51%	50%	54%	52%	37%	33%	35%

*Patients with B-cell lymphoma received R-GDP or R-DHAP. †Used for baseline characteristics. ‡Used for efficacy results. §Two-year estimates were extrapolated from KM curves[2,10,12,17] using the WebPlotDigitizer 4.5 image digitalization tool, as follows: EFS, Figure 1, Supplement[17]; Figure 3C and Figure 3D[10]; OS, Figure 2B[2]; Figure 2, Supplement[17]; Figure 3A[10]; Figure S1B Supplement[12].

‖Includes 2 patients in ZUMA-7 who received ASCT off protocol.

1L, first-line; ASCT, autologous stem cell transplant; Axi, axicabtagene ciloleucel; chemo, chemotherapy; CORAL, Collaborative Trial in Relapsed Aggressive Lymphoma; CR, complete response; CRu, complete response unconfirmed; EFS, event-free survival; FU, follow-up; HDT, high-dose therapy; ITT, intent to treat; KM, Kaplan Meier; KME, KM estimate; NA; not applicable; O-DHAP, ofatumumab plus dexamethasone cytarabine cisplatin; ORCHARRD, Ofatumumab versus Ritixumab Salvage Chemoimmunotherapy in R/R DLBCL; ORR, objective response rate; OS, overall survival; R, refractory; r, relapsed; R-DHAP, rituximab plus dexamethasone cytarabine cisplatin; R-GDP, rituximab plus gemcitabine, dexamethasone, and cisplatin/carboplatin; R-ICE, rituximab plus ifosfamide, carboplatin, and etoposide; sAAIPI, second-line age-adjusted International Prognostic Index; SOC, standard of care.

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