

A SPECIAL MEETING REVIEW EDITION

Highlights in CAR T-Cell Therapy From the 61st American Society of Hematology Annual Meeting

A Review of Selected Presentations From the 61st ASH Meeting

• December 7-10, 2019 • Orlando, Florida

Special Reporting on:

- CD19-Loss With Preservation of Other B-Cell Lineage Features in Patients With Large B-Cell Lymphoma Who Relapsed Post-Axi-Cel
- Pivotal Safety and Efficacy Results From TRANSCEND NHL 001, a Multicenter Phase 1 Study of Lisocabtagene Maraleucel in Relapsed/Refractory Large B-Cell Lymphomas
- KTE-X19, an Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy, in Patients With Relapsed/Refractory Mantle Cell Lymphoma: Results of the Phase 2 ZUMA-2 Study
- Earlier Steroid Use With Axicabtagene Ciloleucel (Axi-Cel) in Patients With Relapsed/Refractory Large B-Cell Lymphoma
- Characteristics and Outcomes of Patients Receiving Bridging Therapy While Awaiting Manufacture of Standard of Care Axicabtagene Ciloleucel CD19 Chimeric Antigen Receptor (CAR) T-Cell Therapy for Relapsed/Refractory Large B-Cell Lymphoma: Results From the US Lymphoma CAR-T Consortium
- Real-World Data of High-Grade Lymphoma Patients Treated With CD19 CAR-T in England
- Post-Marketing Use Outcomes of an Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy, Axicabtagene Ciloleucel, for the Treatment of Large B-Cell Lymphoma in the United States
- Tisagenlecleucel Chimeric Antigen Receptor T-Cell Therapy for Adults With Diffuse Large B-Cell Lymphoma: Real World Experience From the Center for International Blood & Marrow Transplant Research Cellular Therapy Registry

PLUS Meeting Abstract Summaries

With Expert Commentary by:

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ON THE WEB:
hematologyandoncology.net

For adult patients with relapsed/refractory large B-cell lymphoma after ≥2 lines of systemic therapy:

RELAPSE IS LIFE-CHANGING.

SO, YOU CHOSE YESCARTA®.



BEFORE.

Relapse 3 years ago



AND AFTER.

72% ORR | 51% CR¹
with an 11.6-month median follow-up



AND AFTER.

25.8-month median OS with
a 39.1-month median follow-up^{2*†}

YESCARTA CAR T THERAPY, MANUFACTURED RAPIDLY AND RELIABLY¹

In the ZUMA-1 pivotal trial, Kite demonstrated 17 days turnaround time and 99% success in manufacturing T cells.[‡]

[‡]Data reflect results from the ZUMA-1 pivotal trial. The median time from leukapheresis to product delivery.

INDICATION

YESCARTA is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Limitation of Use: YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGIC TOXICITIES

- Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving YESCARTA. Do not administer YESCARTA to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.
- Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving YESCARTA, including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with YESCARTA. Provide supportive care and/or corticosteroids as needed.
- YESCARTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA REMS.

CYTOKINE RELEASE SYNDROME (CRS): CRS occurred in 94% of patients, including 13% with ≥ Grade 3. Among patients who died after receiving YESCARTA, 4 had ongoing CRS at death. The median time to onset was 2 days (range: 1-12 days) and median duration was 7 days (range: 2-58 days). Key manifestations include fever (78%), hypotension (41%), tachycardia (28%), hypoxia (22%), and chills (20%).

Serious events that may be associated with CRS include cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome. Ensure that 2 doses of tocilizumab are available prior to infusion of YESCARTA. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for 4 weeks after infusion. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time. At the first sign of CRS, institute treatment with supportive care, tocilizumab or tocilizumab and corticosteroids as indicated.

NEUROLOGIC TOXICITIES: Neurologic toxicities occurred in 87% of patients. Ninety-eight percent of all neurologic toxicities occurred within the first 8 weeks, with a median time to onset of 4 days (range: 1-43 days) and a median duration of 17 days. Grade 3 or higher occurred in 31% of patients. The most common neurologic toxicities included encephalopathy (57%), headache (44%), tremor (31%), dizziness (21%), aphasia (18%), delirium (17%), insomnia (9%) and anxiety (9%). Prolonged encephalopathy lasting up to 173 days was noted. Serious events including leukoencephalopathy and seizures occurred with YESCARTA. Fatal and serious cases of cerebral edema have occurred in patients treated with YESCARTA. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of neurologic toxicities. Monitor patients for signs or symptoms of neurologic toxicities for 4 weeks after infusion and treat promptly.

YESCARTA REMS: Because of the risk of CRS and neurologic toxicities, YESCARTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA REMS. The required components of the YESCARTA REMS are: Healthcare facilities that dispense and administer YESCARTA

COMPELLING RESPONSE RATES¹

Pivotal analysis with a median 11.6-month follow-up

- ▶ 72% objective response rate (ORR)
 - Median duration of response (DOR): 9.2 months
- ▶ 51% complete remission (CR)
 - Median DOR not reached

LONGER-TERM
FOLLOW-UP

47%
ALIVE
AT 3 YEARS^{2*†}

*ZUMA-1 was a phase 2, open-label, single-arm, multicenter pivotal trial in 101 adults with relapsed or refractory large B-cell lymphoma. For FDA approval, efficacy was established on the basis of CR rate and DOR, as determined by an independent review committee.^{1,3}

†Overall survival (OS) was a secondary endpoint.³ OS data are descriptive and should be carefully interpreted in light of the single-arm design. OS data are not included in the Prescribing Information for YESCARTA®. Not all data continued to be captured at the 3-year follow-up; only OS, investigator-assessed response, and adverse event reporting were captured.²

SAFETY PROFILE

- Cytokine release syndrome (CRS): Grade ≥ 3 incidence, 13%; overall incidence, 94%¹
- Neurologic toxicities: Grade ≥ 3 incidence, 31%; overall incidence, 87%¹
- At the 2-year follow-up, no new serious adverse events, and no new onset of CRS or neurological events, have been reported related to YESCARTA³

LEARN MORE ABOUT YESCARTA RESULTS AT YESCARTAHCP.COM

IMPORTANT SAFETY INFORMATION (continued)

must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of 2 doses of tocilizumab are available for each patient for infusion within 2 hours after YESCARTA infusion, if needed for treatment of CRS. Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer YESCARTA are trained about the management of CRS and neurologic toxicities. Further information is available at www.YESCARTAREMS.com or 1-844-454-KITE (5483).

HYPERSENSITIVITY REACTIONS: Allergic reactions may occur. Serious hypersensitivity reactions including anaphylaxis may be due to dimethyl sulfoxide (DMSO) or residual gentamicin in YESCARTA.

SERIOUS INFECTIONS: Severe or life-threatening infections occurred. Infections (all grades) occurred in 38% of patients, and in 23% with \geq Grade 3. Grade 3 or higher infections with an unspecified pathogen occurred in 16% of patients, bacterial infections in 9%, and viral infections in 4%. YESCARTA should not be administered to patients with clinically significant active systemic infections. Monitor patients for signs and symptoms of infection before and after YESCARTA infusion and treat appropriately. Administer prophylactic anti-microbials according to local guidelines. Febrile neutropenia was observed in 36% of patients and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids and other supportive care as medically indicated. Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs directed against B cells. Perform screening for HBV, HCV, and HIV in accordance with clinical guidelines before collection of cells for manufacturing.

PROLONGED CYTOPENIAS: Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and YESCARTA infusion. Grade 3 or higher cytopenias not resolved by Day 30 following YESCARTA infusion occurred in 28% of patients and included thrombocytopenia (18%), neutropenia (15%), and anemia (3%). Monitor blood counts after YESCARTA infusion.

HYPGAMMAGLOBULINEMIA: B-cell aplasia and hypogammaglobulinemia can occur. Hypogammaglobulinemia occurred in 15% of patients. Monitor immunoglobulin levels

after treatment and manage using infection precautions, antibiotic prophylaxis and immunoglobulin replacement. The safety of immunization with live viral vaccines during or following YESCARTA treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during YESCARTA treatment, and until immune recovery following treatment.

SECONDARY MALIGNANCIES: Patients may develop secondary malignancies. Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact Kite at 1-844-454-KITE (5483) to obtain instructions on patient samples to collect for testing.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES: Due to the potential for neurologic events, including altered mental status or seizures, patients are at risk for altered or decreased consciousness or coordination in the 8 weeks following YESCARTA infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, during this initial period.

ADVERSE REACTIONS: The most common adverse reactions (incidence $\geq 20\%$) include CRS, fever, hypotension, encephalopathy, tachycardia, fatigue, headache, decreased appetite, chills, diarrhea, febrile neutropenia, infections-pathogen unspecified, nausea, hypoxia, tremor, cough, vomiting, dizziness, constipation, and cardiac arrhythmias.

Please see Brief Summary of Prescribing Information, including **BOXED WARNING** and Medication Guide, on the following pages.

References: 1. YESCARTA [package insert]. Santa Monica, CA: Kite Pharma, Inc; 2019. 2. Data on file. Kite Pharma, Inc. 3. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. *Lancet Oncol*. 2019;20(1):31-42.

 **YESCARTA**[®]
(axicabtagene ciloleucel) Suspension
for IV infusion

BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR YESCARTA® (axicabtagene ciloleuce) suspension for intravenous infusion
SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITIES

- **Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving YESCARTA. Do not administer YESCARTA to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids [see Dosage and Administration (2.2, 2.3), Warnings and Precautions (5.1)].**
- **Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving YESCARTA, including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with YESCARTA. Provide supportive care and/or corticosteroids, as needed [see Dosage and Administration (2.2, 2.3), Warnings and Precautions (5.2)].**
- **YESCARTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA REMS [see Warnings and Precautions (5.3)].**

1 INDICATIONS AND USAGE

YESCARTA is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Limitation of Use: YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma.

2 DOSAGE AND ADMINISTRATION

2.2 Administration: YESCARTA is for autologous use only. The patient's identity must match the patient identifiers on the YESCARTA cassette and infusion bag. Do not infuse YESCARTA if the information on the patient-specific label does not match the intended patient [see Dosage and Administration(2.2.3)].

Preparing Patient for YESCARTA Infusion: Confirm availability of YESCARTA prior to starting the lymphodepleting regimen. **Pre-treatment:** Administer a lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m² intravenously and fludarabine 30 mg/m² intravenously on the fifth, fourth, and third day before infusion of YESCARTA. **Premedication:** Administer acetaminophen 650 mg PO and diphenhydramine 12.5 mg intravenously or PO approximately 1 hour before YESCARTA infusion. Avoid prophylactic use of systemic corticosteroids, as it may interfere with the activity of YESCARTA.

Preparation of YESCARTA for Infusion: Coordinate the timing of YESCARTA thaw and infusion. Confirm the infusion time in advance, and adjust the start time of YESCARTA thaw such that it will be available for infusion when the patient is ready. Confirm patient identity: Prior to YESCARTA preparation, match the patient's identity with the patient identifiers on the YESCARTA cassette. Do not remove the YESCARTA product bag from the cassette if the information on the patient-specific label does not match the intended patient. Once patient identification is confirmed, remove the YESCARTA product bag from the cassette and check that the patient information on the cassette label matches the bag label. Inspect the product bag for any breaches of container integrity such as breaks or cracks before thawing. If the bag is compromised, follow the local guidelines (or call Kite at 1-844-454-KITE). Place the infusion bag inside a second sterile bag per local guidelines. Thaw YESCARTA at approximately 37°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Do not wash, spin down, and/or re-suspend YESCARTA in new media prior to infusion. Once thawed, YESCARTA may be stored at room temperature (20°C to 25°C) for up to 3 hours.

Administration: For autologous use only. Ensure that tocilizumab and emergency equipment are available prior to infusion and during the recovery period. Do NOT use a leukodepleting filter. Central venous access is recommended for the infusion of YESCARTA. Confirm the patient's identity matches the patient identifiers on the YESCARTA product bag. Prime the tubing with normal saline prior to infusion. Infuse the entire contents of the YESCARTA bag within 30 minutes by either gravity or a peristaltic pump. YESCARTA is stable at room temperature for up to 3 hours after thaw. Gently agitate the product bag during YESCARTA infusion to prevent cell clumping. After the entire content of the product bag is infused, rinse the tubing with normal saline at the same infusion rate to ensure all product is delivered. YESCARTA contains human blood cells that are genetically modified with

replication incompetent retroviral vector. Follow universal precautions and local biosafety guidelines for handling and disposal to avoid potential transmission of infectious diseases.

Monitoring: Administer YESCARTA at a certified healthcare facility. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS and neurologic toxicities. Instruct patients to remain within proximity of the certified healthcare facility for at least 4 weeks following infusion.

2.3 Management of Severe Adverse Reactions

Cytokine Release Syndrome (CRS): Identify CRS based on clinical presentation [see Warnings and Precautions (5.1)]. Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in Table 1. Patients who experience Grade 2 or higher CRS (e.g., hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life-threatening CRS, consider intensive care supportive therapy.

Table 1. CRS Grading and Management Guidance

CRS Grade (a)	Tocilizumab	Corticosteroids
Grade 1 Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).	N/A	N/A
Grade 2 Symptoms require and respond to moderate intervention. Oxygen requirement less than 40% FiO ₂ or hypotension responsive to fluids or low-dose of one vasopressor or Grade 2 organ toxicity (b).	Administer tocilizumab (c) 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). If no clinical improvement in the signs and symptoms of CRS after the first dose, repeat tocilizumab every 8 hours as needed. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab.
Grade 3 Symptoms require and respond to aggressive intervention. Oxygen requirement greater than or equal to 40% FiO ₂ or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis.	Per Grade 2	Administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (e.g., 10 mg intravenously every 6 hours). Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days.
Grade 4 Life-threatening symptoms. Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD) or Grade 4 organ toxicity (excluding transaminitis).	Per Grade 2	Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above.

(a) Lee et al 2014, (b) Refer to Table 2 for management of neurologic toxicity, (c) Refer to tocilizumab Prescribing Information for details

Neurologic Toxicity: Monitor patients for signs and symptoms of neurologic toxicities (Table 2). Rule out other causes of neurologic symptoms. Patients who experience Grade 2 or higher neurologic toxicities should be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive care supportive therapy for severe or life threatening neurologic toxicities. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis for any Grade 2 or higher neurologic toxicities.

Table 2. Neurologic Toxicity Grading and Management Guidance

Grading Assessment	Concurrent CRS	No Concurrent CRS
Grade 2	Administer tocilizumab per Table 1 for management of Grade 2 CRS. If no improvement within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenously 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.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 3	Administer tocilizumab per Table 1 for management of Grade 2 CRS. In addition, administer dexamethasone 10 mg intravenously 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.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 4	Administer tocilizumab per Table 1 for management of Grade 2 CRS. Administer methylprednisolone 1000 mg intravenously per day with first dose of tocilizumab and continue methylprednisolone 1000 mg intravenously per day for 2 more days; if improves, then manage as above.	Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	

4 CONTRAINDICATIONS: None.

5 WARNINGS AND PRECAUTIONS

5.1 Cytokine Release Syndrome (CRS): CRS, including fatal or life-threatening reactions, occurred following treatment with YESCARTA. In Study 1, CRS occurred in 94% (101/108) of patients receiving YESCARTA, including ≥ Grade 3 (Lee grading system) CRS in 13% (14/108) of patients. Among patients who died after receiving YESCARTA, four had ongoing CRS events at the time of death. The median time to onset was 2 days (range: 1 to 12 days) and the median duration of CRS was 7 days (range: 2 to 58 days). Key manifestations of CRS include fever (78%), hypotension (41%), tachycardia (28%), hypoxia (22%), and chills (20%). Serious events that may be associated with CRS include cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) [see *Adverse Reactions (6)*]. Ensure that 2 doses of tocilizumab are available prior to infusion of YESCARTA. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for 4 weeks after infusion. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time [see *Patient Counseling Information (17)*]. At the first sign of CRS, institute treatment with supportive care, tocilizumab or tocilizumab and corticosteroids as indicated [see *Dosage and Administration (2.3)*].

5.2 Neurologic Toxicities: Neurologic toxicities, that were fatal or life-threatening, occurred following treatment with YESCARTA. Neurologic toxicities occurred in 87% of patients. Ninety-eight percent of all neurologic toxicities occurred within the first 8 weeks of YESCARTA infusion, with a median time to onset of 4 days (range: 1 to 43 days). The median duration of neurologic toxicities was 17 days. Grade 3 or higher neurologic toxicities occurred in 31% of patients. The most common neurologic toxicities included encephalopathy (57%), headache (44%), tremor (31%), dizziness (21%), aphasia (18%), delirium (17%), insomnia (9%) and anxiety (9%). Prolonged encephalopathy lasting up to 173 days was noted. Serious events including leukoencephalopathy and seizures occurred with YESCARTA. Fatal and serious cases of cerebral edema have occurred in patients treated with YESCARTA. Monitor patients

at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of neurologic toxicities. Monitor patients for signs or symptoms of neurologic toxicities for 4 weeks after infusion and treat promptly [see *Management of Severe Adverse Reactions (2.3); Neurologic Toxicities*].

5.3 YESCARTA REMS: Because of the risk of CRS and neurologic toxicities, YESCARTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA REMS [see *Boxed Warning and Warnings and Precautions (5.1 and 5.2)*]. The required components of the YESCARTA REMS are:

- Healthcare facilities that dispense and administer YESCARTA must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of two doses of tocilizumab are available for each patient for infusion within 2 hours after YESCARTA infusion, if needed for treatment of CRS.
- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer YESCARTA are trained about the management of CRS and neurologic toxicities.

Further information is available at www.YescartaREMS.com or 1-844-454-KITE (5483).

5.4 Hypersensitivity Reactions: Allergic reactions may occur with the infusion of YESCARTA. Serious hypersensitivity reactions including anaphylaxis, may be due to dimethyl sulfoxide (DMSO) or residual gentamicin in YESCARTA.

5.5 Serious Infections: Severe or life-threatening infections occurred in patients after YESCARTA infusion. In Study 1, infections (all grades) occurred in 38% of patients. Grade 3 or higher infections occurred in 23% of patients. Grade 3 or higher infections with an unspecified pathogen occurred in 16% of patients, bacterial infections in 9%, and viral infections in 4%. YESCARTA should not be administered to patients with clinically significant active systemic infections. Monitor patients for signs and symptoms of infection before and after YESCARTA infusion and treat appropriately. Administer prophylactic anti-microbials according to local guidelines. Febrile neutropenia was observed in 36% of patients after YESCARTA infusion and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids and other supportive care as medically indicated. *Viral Reactivation:* Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs directed against B cells. Perform screening for HBV, HCV, and HIV in accordance with clinical guidelines before collection of cells for manufacturing.

5.6 Prolonged Cytopenias: Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and YESCARTA infusion. In Study 1, Grade 3 or higher cytopenias not resolved by Day 30 following YESCARTA infusion occurred in 28% of patients and included thrombocytopenia (18%), neutropenia (15%), and anemia (3%). Monitor blood counts after YESCARTA infusion.

5.7 Hypogammaglobulinemia: B-cell aplasia and hypogammaglobulinemia can occur in patients receiving treatment with YESCARTA. In Study 1, hypogammaglobulinemia occurred in 15% of patients. Monitor immunoglobulin levels after treatment with YESCARTA and manage using infection precautions, antibiotic prophylaxis and immunoglobulin replacement. The safety of immunization with live viral vaccines during or following YESCARTA treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during YESCARTA treatment, and until immune recovery following treatment with YESCARTA.

5.8 Secondary Malignancies: Patients treated with YESCARTA may develop secondary malignancies. Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact Kite at 1-844-454-KITE (5483) to obtain instructions on patient samples to collect for testing.

5.9 Effects on Ability to Drive and Use Machines: Due to the potential for neurologic events, including altered mental status or seizures, patients receiving YESCARTA are at risk for altered or decreased consciousness or coordination in the 8 weeks following YESCARTA infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, during this initial period.

6 ADVERSE REACTIONS: The following adverse reactions are described in Warnings and Precautions: Cytokine Release Syndrome, Neurologic Toxicities, Hypersensitivity Reactions, Serious Infections, Prolonged Cytopenias, Hypogammaglobulinemia.

6.1 Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety data described in this section reflect exposure to YESCARTA in the clinical trial (Study 1) in which 108 patients with relapsed/refractory B-cell NHL received CAR-positive T cells based on a recommended dose which was weight-based [see *Clinical Trials (14)*]. Patients with a history of CNS disorders (such as seizures or cerebrovascular ischemia) or autoimmune disease requiring systemic immunosuppression were ineligible. The median duration of follow up was 8.7 months. The median age of the study population was 58 years (range: 23 to 76 years); 68% were men. The baseline ECOG performance status was

43% with ECOG 0, and 57% with ECOG 1. The most common adverse reactions (incidence $\geq 20\%$) include CRS, fever, hypotension, encephalopathy, tachycardia, fatigue, headache, decreased appetite, chills, diarrhea, febrile neutropenia, infections-pathogen unspecified, nausea, hypoxia, tremor, cough, vomiting, dizziness, constipation, and cardiac arrhythmias. Serious adverse reactions occurred in 52% of patients. The most common serious adverse reactions ($> 2\%$) include encephalopathy, fever, lung infection, febrile neutropenia, cardiac arrhythmia, cardiac failure, urinary tract infection, renal insufficiency, aphasia, cardiac arrest, *Clostridium difficile* infection, delirium, hypotension, and hypoxia. The most common ($\geq 10\%$) Grade 3 or higher reactions include febrile neutropenia, fever, CRS, encephalopathy, infections-pathogen unspecified, hypotension, hypoxia, and lung infections. Forty-five percent (49/108) of patients received tocilizumab after infusion of YESCARTA.

Summary of Adverse Reactions Observed in at Least 10% of the Patients Treated with YESCARTA in Study 1

Adverse Reaction		Any Grade (%)	Grades 3 or Higher (%)
Blood and lymphatic system disorders	Febrile neutropenia	34	31
Cardiac disorders	Tachycardia	57	2
	Arrhythmia	23	7
Gastrointestinal disorders	Diarrhea	38	4
	Nausea	34	0
	Vomiting	26	1
	Constipation	23	0
	Abdominal pain	14	1
	Dry mouth	11	0
General disorders and administration site conditions	Fever	86	16
	Fatigue	46	3
	Chills	40	0
	Edema	19	1
Immune system disorders	Cytokine release syndrome	94	13
	Hypogammaglobulinemia	15	0
Infections and infestations	Infections-pathogen unspecified	26	16
	Viral infections	16	4
	Bacterial infections	13	9
Investigations	Decreased appetite	44	2
	Weight decreased	16	0
	Dehydration	11	3
Musculoskeletal and connective tissue disorders	Motor dysfunction	19	1
	Pain in extremity	17	2
	Back pain	15	1
	Muscle pain	14	1
	Arthralgia	10	0
Nervous system disorders	Encephalopathy	57	29
	Headache	45	1
	Tremor	31	2
	Dizziness	21	1
	Aphasia	18	6
Psychiatric disorders	Delirium	17	6
Respiratory, thoracic and mediastinal disorders	Hypoxia	32	11
	Cough	30	0
	Dyspnea	19	3
	Pleural effusion	13	2
Renal and urinary disorders	Renal insufficiency	12	5
Vascular disorders	Hypotension	57	15
	Hypertension	15	6
	Thrombosis	10	1

The following events were also counted in the incidence of CRS: tachycardia, arrhythmia, fever, chills, hypoxemia, renal insufficiency, and hypotension. For a complete list of events that contributed to the incidence of certain adverse reactions, please see footnote below Table 3 in Section 6.1 of the Full Prescribing Information.

Other clinically important adverse reactions that occurred in less than 10% of patients treated with YESCARTA include the following: blood and lymphatic system disorders: coagulopathy (2%); cardiac disorders: cardiac failure (6%) and cardiac arrest (4%); immune system disorders: hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) (1%), hypersensitivity (1%); infections and infestations disorders: fungal infections (5%); nervous system disorders: ataxia

(6%), seizure (4%), dyscalculia (2%), and myoclonus (2%); respiratory, thoracic and mediastinal disorders: pulmonary edema (9%); skin and subcutaneous tissue disorders: rash (9%); vascular disorders: capillary leak syndrome (3%).

Grade 3 or 4 Laboratory Abnormalities Occurring in $\geq 10\%$ of Patients in Study 1 Following Treatment with YESCARTA based on CTCAE (N=108)

Lymphopenia 100%, Leukopenia 96%, Neutropenia 93%, Anemia 66%, Thrombocytopenia 58%, Hypophosphatemia 50%, Hyponatremia 19%, Uric acid increased 13%, Direct Bilirubin increased 13%, Hypokalemia 10%, Alanine Aminotransferase increased 10%.

6.2 Immunogenicity: YESCARTA has the potential to induce anti-product antibodies. The immunogenicity of YESCARTA has been evaluated using an enzyme-linked immunosorbent assay (ELISA) for the detection of binding antibodies against FMC63, the originating antibody of the anti-CD19 CAR. Three patients tested positive for pre-dose anti-FMC63 antibodies at baseline and Months 1, 3, or 6 in Study 1. There is no evidence that the kinetics of initial expansion and persistence of YESCARTA, or the safety or effectiveness of YESCARTA, was altered in these patients.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Risk Summary: There are no available data with YESCARTA use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with YESCARTA to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known if YESCARTA has the potential to be transferred to the fetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia. Therefore, YESCARTA is not recommended for women who are pregnant, and pregnancy after YESCARTA infusion should be discussed with the treating physician. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% - 4% and 15% - 20%, respectively.

8.2 Lactation: Risk Summary: There is no information regarding the presence of YESCARTA in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for YESCARTA and any potential adverse effects on the breastfed infant from YESCARTA or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential: Pregnancy Testing: Pregnancy status of females with reproductive potential should be verified. Sexually-active females of reproductive potential should have a pregnancy test prior to starting treatment with YESCARTA. **Contraception:** See the prescribing information for fludarabine and cyclophosphamide for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy. There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with YESCARTA. **Infertility:** There are no data on the effect of YESCARTA on fertility.

8.4 Pediatric Use: The safety and efficacy of YESCARTA have not been established in pediatric patients.

8.5 Geriatric Use: Clinical trials of YESCARTA did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently or have different safety outcomes as compared to younger patients.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide). Ensure that patients understand the risk of manufacturing failure (1% in clinical trial). In case of a manufacturing failure, a second manufacturing of YESCARTA may be attempted. In addition, while the patient awaits the product, additional chemotherapy (not the lymphodepletion) may be necessary and may increase the risk of adverse events during the pre-infusion period. Advise patients to seek immediate attention for any of the following: Cytokine Release Syndrome, Neurologic Toxicities, Serious Infections, Prolonged Cytopenia [see Warnings and Precautions (5.1, 5.2, 5.3, 5.5) and Adverse Reactions (6) for more information and signs and symptoms]. Advise patients for the need to: Refrain from driving or operating heavy or potentially dangerous machinery after YESCARTA infusion until at least 8 weeks after infusion [see Warnings and Precautions (5.2)], Have periodic monitoring of blood counts. Contact Kite at 1-844-454-KITE (5483) if they are diagnosed with a secondary malignancy [see Warnings and Precautions (5.8)].

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CD19-Loss With Preservation of Other B-Cell Lineage Features in Patients With Large B-Cell Lymphoma Who Relapsed Post-Axi-Cel

The multicenter, single-arm phase 1/2 ZUMA-1 study (Safety and Efficacy of KTE-C19 in Adults With Refractory Aggressive Non-Hodgkin Lymphoma) evaluated axicabtagene ciloleucel in patients with refractory large B-cell lymphoma.^{1,2} The phase 2 portion of the trial originally enrolled 111 patients into 2 cohorts. The 77 patients in cohort 1 had diffuse large B-cell lymphoma (DLBCL), and the 24 patients in cohort 2 had primary mediastinal B-cell lymphoma or transformed follicular lymphoma. The primary endpoint was the objective response rate (ORR). After a median follow-up of 27.1 months, the ORR was 83%, with a complete response (CR) rate of 58%. The 2-year rate of progression-free survival (PFS) was 39%. The 2-year rate of overall survival (OS) was 51%. The median OS was not reached. After a median follow-up of 39.1 months, the 3-year OS rate was 47%.

Approximately 60% of patients relapse or progress after treatment with

axicabtagene ciloleucel.¹ Mechanisms that enable relapse may include loss or modification of CD19 and involvement of the immune tumor environment.³ To gain further insight regarding mechanisms of treatment failure after axicabtagene ciloleucel infusion, a post-hoc analysis analyzed tumor tissue obtained from patients in cohorts 1 and 2 in the ZUMA-1 trial who responded and subsequently relapsed.⁴ The protein expression of markers of B-cell lineage was centrally assessed with immunohistochemistry (IHC). For select cases, IHC was followed by immunofluorescence staining and confocal microscopy. Assessed markers included CD19 (cytoplasmic domain), CD20 (cytoplasmic domain), CD22 (surface domain), CD79a (surface domain), and PAX5 (nuclear stain). CD19 splice variants were evaluated by RNA sequencing. Tumor samples included 82 with pretreatment IHC, 18 IHC samples from patients who initially responded and then relapsed, 16 paired samples (pre- and postrelapse)

with IHC, and 5 paired samples with RNA sequencing.

A consistent axicabtagene ciloleucel treatment effect was observed across all baseline levels of CD19. Median baseline CD19 H-scores were 200 for the 49 patients with a CR as the best response, 260 for the 22 patients with a partial response, and 250 for the 11 patients with stable or progressive disease (Figure 1). The median H-score was 190 in 32 patients with an ongoing response and 240 in 35 patients who had relapsed. Prior to treatment, 90% of tumor biopsies were positive for CD19, and 96% were positive for CD20. Expression of CD19 and/or CD20 was reported in 98% of samples. All 13 patients with CD19-positive samples had relapsed within 6 months of receiving axicabtagene ciloleucel therapy. The 5 patients with CD19-negative samples had a more varied course, with relapses observed between approximately 2 months and 15 months. Among 18 biopsies taken after progression, 5 (28%) did

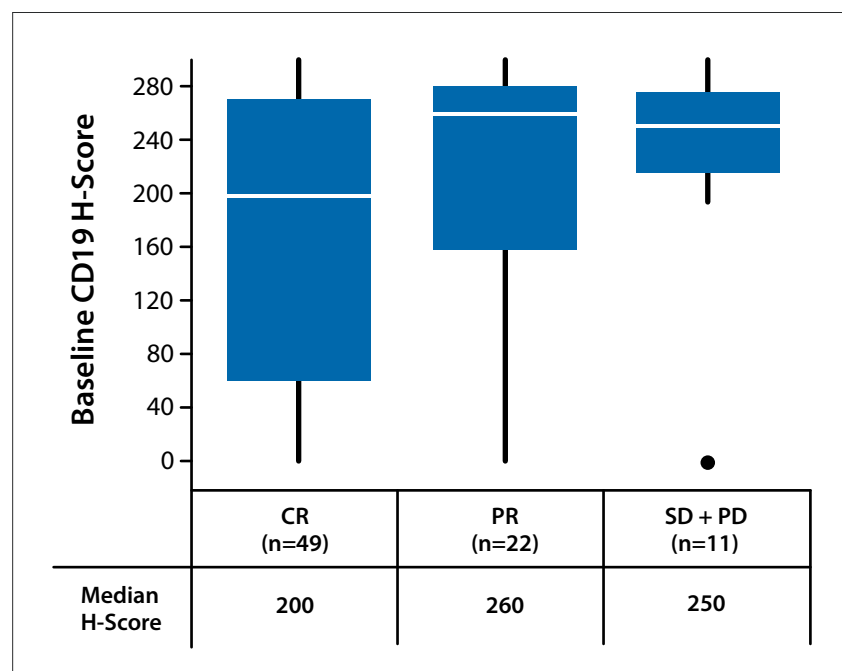


Figure 1. Best response according to baseline CD19 H-score in a post-hoc analysis of patients treated with axicabtagene ciloleucel in the ZUMA-1 trial who responded and subsequently relapsed. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; ZUMA-1, Safety and Efficacy of KTE-C19 in Adults With Refractory Aggressive Non-Hodgkin Lymphoma. Adapted from Neelapu SS et al. ASH abstract 203. *Blood*. 2019;134(suppl 1).³

not express CD19; however, all of the samples showed at least minimal expression of the other B-cell antigens. Among the 18 postprogression biopsy samples, 72% expressed CD19, 94% expressed CD22, and 100% expressed CD20, CD79a, and PAX5. Among the 16 paired samples, 4 (25%) showed a loss of CD19 expression at the time of relapse (Figure 2). Downregulation of CD19 was demonstrated by RNA sequencing in 1 patient.

IHC showed expression of CD20 in all samples at relapse. A combination of immunofluorescence and confocal microscopy showed that CD20 expression was maintained on the cell membrane at progression. CD20 expression was of particular interest because patients had received previous treatment with rituximab.

A separate study of pediatric patients with acute lymphoblastic leukemia who received treatment with chimeric antigen receptor (CAR) T-cell therapy showed that alternative splicing of CD19 could result in expression of a truncated CD19 variant that provided some CD19 activity, but failed to trigger killing by CD19-directed CAR T-cell therapy.⁵ Samples from the ZUMA-1 study also revealed alternative splicing, with loss of exon 2 and/or exons 5 and 6. Alternative splicing events were significantly different in baseline samples vs those obtained after relapse ($P < .05$). Taken together, the results suggest that the efficacy of CD19-directed CAR T-cell therapy could potentially be improved by simultaneous or sequential targeting of CD19 plus other B-cell antigens.

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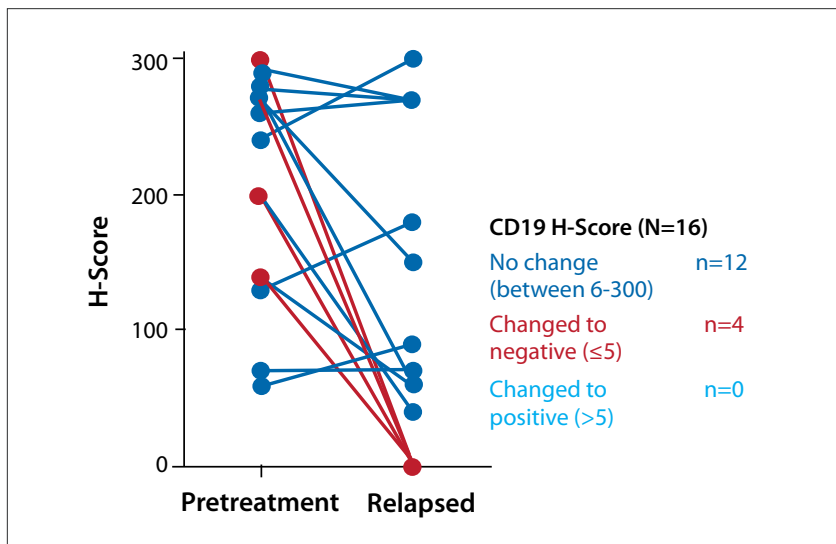


Figure 2. Changes in the H-score in a post-hoc analysis of patients treated with axicabtagene ciloleucel in the ZUMA-1 trial who responded and subsequently relapsed. ZUMA-1, Safety and Efficacy of KTE-C19 in Adults With Refractory Aggressive Non-Hodgkin Lymphoma. Adapted from Neelapu SS et al. ASH abstract 203. *Blood*. 2019;134(suppl 1).³

Pivotal Safety and Efficacy Results From TRANSCEND NHL 001, a Multicenter Phase 1 Study of Lisocabtagene Maraleucel in Relapsed/Refractory Large B-Cell Lymphomas

Lisocabtagene maraleucel is a CD19-directed CAR T-cell product that contains a 4-1BB costimulatory domain to increase T-cell proliferation and persistence.¹ The product is administered using a defined ratio of CD4-positive and CD8-

positive CAR T cells. The multicenter phase 1 TRANSCEND NHL 001 trial (Study Evaluating the Safety and Pharmacokinetics of JCAR017 in B-Cell Non-Hodgkin Lymphoma) evaluated lisocabtagene maraleucel in adults with relapsed or refractory large B-cell lym-

phoma.² Patients in the DLBCL cohort had relapsed or refractory DLBCL—not otherwise specified, including transformed indolent lymphoma; high-grade B-cell lymphoma with MYC and the BCL2 and/or BCL6 rearrangements; primary mediastinal B-cell

lymphoma; or follicular lymphoma of grade 3B. Patients had received at least 2 prior lines of therapy and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. The study permitted enrollment of patients who had undergone prior autologous or allogeneic stem cell transplant (SCT), as well as those with secondary central nervous system (CNS) lymphoma.

Bridging therapy was allowed after leukapheresis; however, patients were required to have a positive positron emission tomography result prior to lymphodepletion. Lymphodepletion was accomplished with a 3-day regimen of fludarabine (30 mg/m²) plus cyclophosphamide (300 mg/m²). Lisocabtagene maraleucel was administered within a week of lymphodepletion. In the dose-finding portion of the

study, lisocabtagene maraleucel was administered to 60 patients at 3 dose levels: 50 × 10⁶, 100 × 10⁶, or 150 × 10⁶. Among 344 patients who underwent leukapheresis, 294 received an infusion of CAR T cells. Lisocabtagene maraleucel with conforming product was administered to 269 patients with large B-cell lymphoma, and 256 were included in the large B-cell lymphoma efficacy set. Forty-six patients received dose level 1, 169 received dose level 2, and 41 received dose level 3.

Among the 269 patients treated with lisocabtagene maraleucel, the median age was 63 years (range, 18-86 years). Fifty-one percent had DLBCL—not otherwise specified, and 3% of all patients had secondary CNS lymphoma. Thirty-eight percent had a high disease burden, and the median number of prior systemic therapies

was 3 (range, 1-8). Two-thirds of patients had chemotherapy-refractory disease, 44% had never achieved a CR with prior treatment, and 59% received bridging therapy during the study. High-risk features associated with shortened OS were noted in 89% of patients.

After a median follow-up of 12.0 months (range, 11.2-16.7 months), the ORR was 73% (95% CI, 67%-78%), with a CR rate of 53% (95% CI, 47%-59%). The median time to first CR or partial response was 1.0 months (range, 0.7-8.9 months). Response durability is shown in Figure 3. Clinically meaningful response rates were observed across all subgroups. Among all patients, 12-month PFS was 44.1% (95% CI, 37.3%-50.7%) and 12-month OS was 57.9% (95% CI, 51.3%-63.8%).

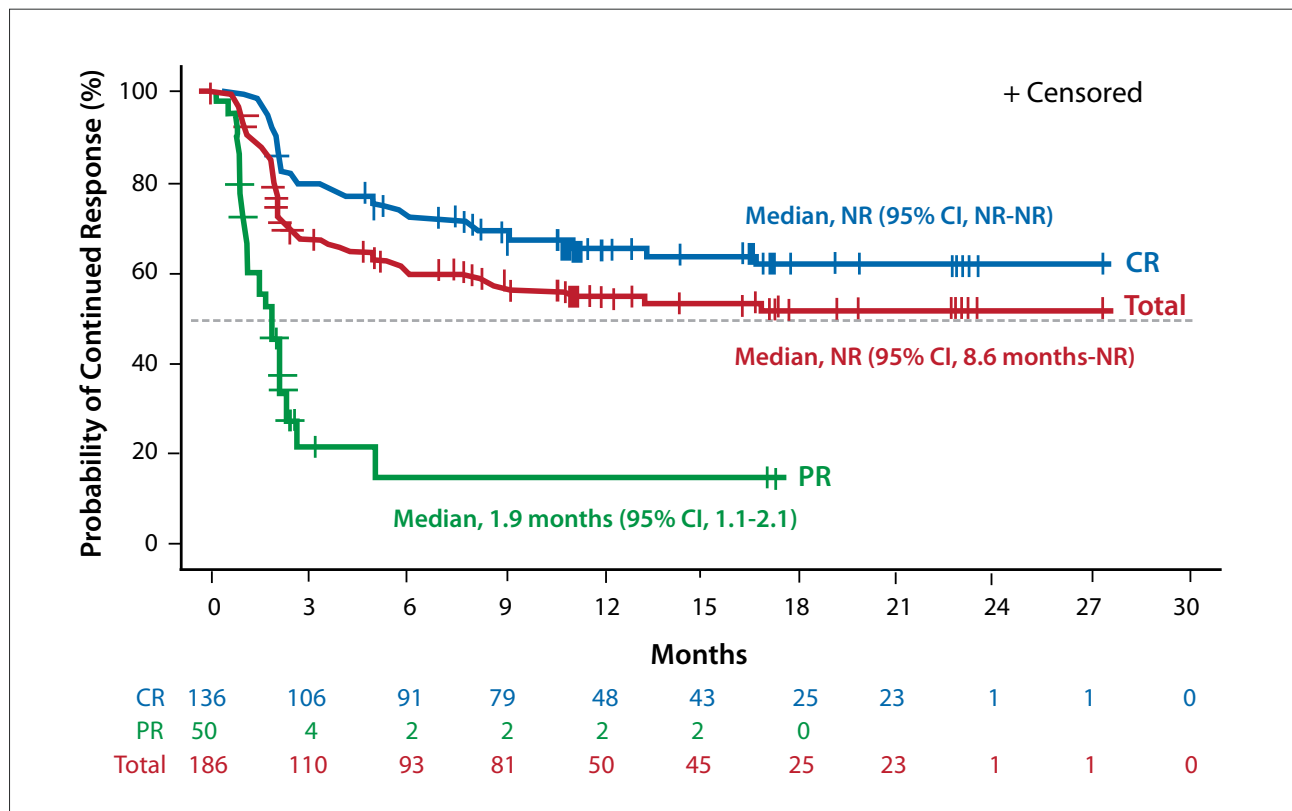


Figure 3. Durability of response in the phase 1 TRANSCEND NHL 001 trial, which evaluated lisocabtagene maraleucel in adults with relapsed or refractory large B-cell lymphoma. CR, complete response; NR, not reached; PR, partial response; TRANSCEND NHL 001, Study Evaluating the Safety and Pharmacokinetics of JCAR017 in B-Cell Non-Hodgkin Lymphoma. Adapted from Abramson JS et al. ASH abstract 241. *Blood*. 2019;134(suppl 1).²

Nearly all patients (99%) developed a treatment-emergent adverse event (AE) of any grade. The most common events were neutropenia (63%), anemia (48%), and fatigue (44%). The most common grade 3/4 AEs were neutropenia (60%), anemia (38%), and thrombocytopenia (27%). Grade 5 treatment-emergent AEs occurred in 7 patients; in 4 patients, these deaths were considered related to lisocabtagene maraleucel. They were caused by diffuse

alveolar damage, pulmonary hemorrhage, multiple organ dysfunction syndrome, and cardiomyopathy.

There were no reports of grade 5 cytokine-release syndrome or neurotoxicity. Any-grade cytokine-release syndrome occurred in 42% of patients, including 1% with grade 3 and 1% with grade 4. Thirty percent of patients developed a neurologic AE of any grade, including 9% with grade 3 and 1% with grade 4. Prolonged infections

of at least grade 3 were reported in 37% of patients, and 12% had infections of grade 3 or higher.

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KTE-X19, an Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy, in Patients With Relapsed/Refractory Mantle Cell Lymphoma: Results of the Phase 2 ZUMA-2 Study

Patients with mantle cell lymphoma who progress after treatment with a Bruton tyrosine kinase (BTK) inhibitor have a median OS of less than 6 months.¹ KTE-X19 is a CD19-directed CAR T-cell therapy that contains a CD3 ζ T-cell activation domain and a CD28-signaling domain. The KTE-X19 CAR T cells are manufactured using a process that removes circulating tumor cells.² The multicenter, international phase 2 ZUMA-2 trial (A Phase 2 Multicenter Study Evaluating Subjects With Relapsed/Refractory Mantle Cell Lymphoma) evaluated KTE-X19 in patients with relapsed or refractory mantle cell lymphoma.³ Enrolled patients had received up to 5 prior therapies, which had to include chemotherapy with an anthracycline or bendamustine, an anti-CD20 monoclonal antibody, and a BTK inhibitor. Patients had at least 1 measurable lesion and an ECOG performance status of 0 or 1. The trial excluded patients who had undergone prior allogeneic SCT or had previously received CD19-targeted therapy or CAR T-cell therapy. After enrollment and leukapheresis, patients could receive bridging therapy with dexamethasone, ibrutinib, or acalabrutinib.

Conditioning chemotherapy consisted of fludarabine (30 mg/m²) plus cyclophosphamide (500 mg/m²) on days -5, -4, and -3. The CAR T cells were administered at a dose of 2×10^6 KTE-X19 cells per kilogram of body weight by means of a single intravenous infusion on day 0. The first tumor assessment occurred on day 28. The primary

endpoint was the ORR as assessed by an independent review committee and included the first 60 patients who received treatment.⁴

Among the 74 patients enrolled in the trial, 69 received conditioning chemotherapy. The KTE-X19 product was successfully manufactured for 71 patients (96%), and 68 patients (92%)

ABSTRACT SUMMARY Circulating DNA for Molecular Response Prediction, Characterization of Resistance Mechanisms and Quantification of CAR T Cells During Axicabtagene Ciloleucel Therapy

A subset of patients with relapsed/refractory DLBCL will develop progressive disease after treatment with axicabtagene ciloleucel. A study evaluated whether cell-free DNA analysis could characterize molecular responses and resistance mechanisms and track CAR19 cells (Abstract 550). The study evaluated plasma samples from 35 patients. Levels of pretreatment circulating tumor DNA were prognostic in patients receiving CAR19 therapy. PFS was significantly higher among patients with low circulating tumor DNA. Early circulating tumor DNA dynamics and day 29 levels correlated with outcomes. Patients with undetectable early circulating tumor DNA had a significantly higher PFS. The study was able to track CAR19 cells using cell-free DNA. Early CAR19 dynamics did not correspond to outcome. Levels of circulating tumor DNA were more predictive of response than levels of axicabtagene ciloleucel. The investigators concluded that baseline and interim circulating tumor DNA measurements have prognostic significance in DLBCL patients undergoing treatment with CAR19 T cells. Cell-free DNA analysis can identify emergent resistance mutations, including in CD19.

received the KTE-X19 infusion. The safety analysis included all 68 patients who received the KTE-X19 infusion. The median time from leukapheresis to delivery of the KTE-X19 cells to the study site was 16 days. The 68 patients were a median age of 65 years (range, 38-79 years), 85% had stage IV disease, and 56% had a Mantle Cell Lymphoma International Prognostic Index score indicating intermediate- or high-risk disease. The median number of prior therapies was 3 (range, 1-5), and 43% had relapsed after autologous SCT. Sixty-eight percent were refractory to treatment with a BTK inhibitor, and 32% had relapsed after treatment. To control disease progression prior to study treatment, 37% of patients received bridging therapy.

After a median follow-up of 12.3 months (range, 7.0-32.3 months), the ORR was 93% (95% CI, 84%-98%) and the CR rate was 67% (95% CI, 53%-78%). The median time to an initial response was 1.0 month (range,

0.8-3.1 months), and the median time to a CR was 3.0 months (range, 0.9-8.3 months). Thirty-five percent of patients converted from a partial response to a CR, and 5% converted from stable disease to a CR. The ORR was consistent across most subgroups. Median PFS and median OS were not reached. Twelve-month PFS was 61% (95% CI, 45%-74%), and 12-month OS was 83% (95% CI, 71%-91%). The median duration of response was not reached (Figure 4). Remission was maintained in 57% of all patients and 78% of patients with a CR. Among the first 28 patients treated, 43% remained in continued remission without additional therapy after a median follow-up of 27.0 months (range, 25.3-32.3 months).

The most common treatment-emergent AEs of any grade included pyrexia (94%), neutropenia (87%), and thrombocytopenia (74%). The most common grade 3/4 hematologic AEs consisted of neutropenia

(85%), thrombocytopenia (51%), and anemia (50%). The most common treatment-emergent grade 3/4 AEs were hypophosphatemia (22%, all grade 3), hypotension (19% grade 3 and 3% grade 4), and hypoxia (12% grade 3 and 9% grade 4). Grade 5 AEs included 1 case of organizing pneumonia on day 37 and 1 case of staphylococcal bacteremia on day 134.

Any-grade cytokine-release syndrome was reported in 91% of patients, including 15% with grade 3/4. No cases of grade 5 cytokine-release syndrome occurred. The median time to onset was 2 days (range, 1-13 days). Management consisted of tocilizumab in 59% of patients and corticosteroids in 22%. Cytokine-release syndrome resolved in all patients, at a median duration of 11 days.

Neurologic AEs of any grade occurred in 63% of patients; they were grade 3/4 in 31%. No grade 5 neurologic AEs occurred. The most common symptoms of neurotoxicity included

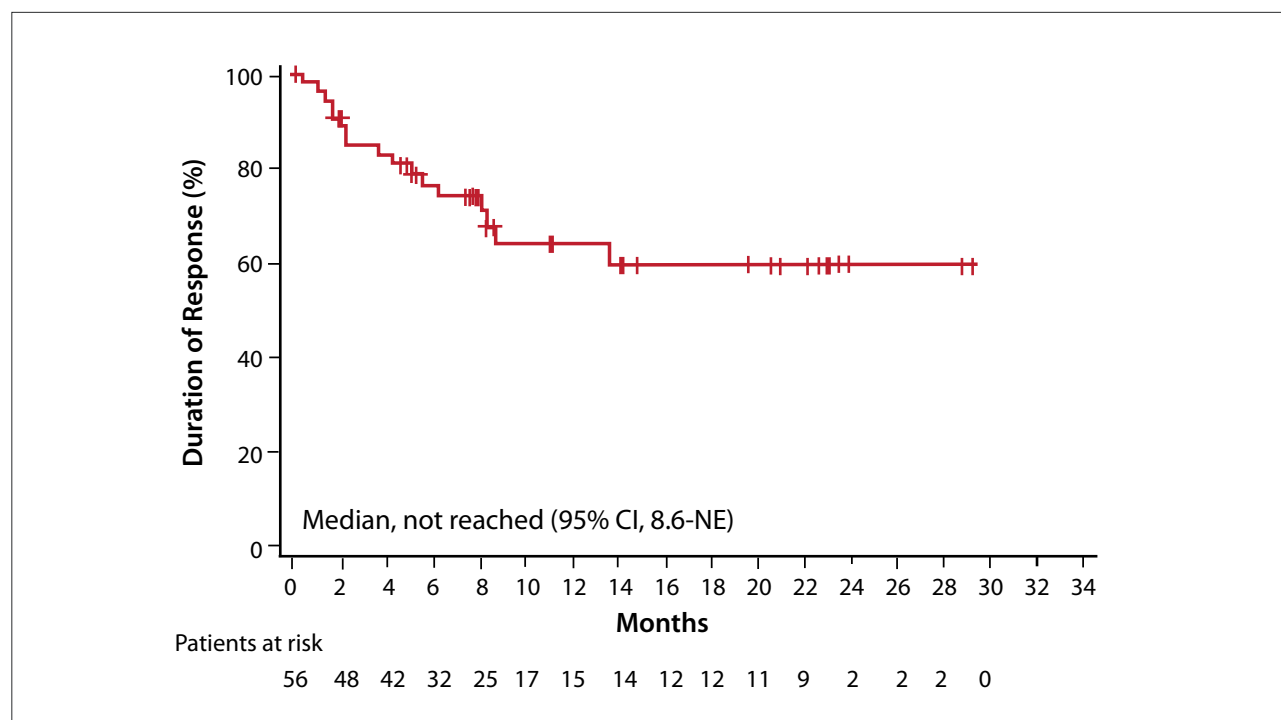


Figure 4. Among patients with mantle cell lymphoma treated with KTE-X19 in the phase 2 ZUMA-2 trial, the median duration of response was not reached. ZUMA-2, A Phase 2 Multicenter Study Evaluating Subjects With Relapsed/Refractory Mantle Cell Lymphoma. Adapted from Wang M et al. ASH abstract 754. *Blood*. 2019;134(suppl 1).³

any-grade tremor (35%), encephalopathy (31%), and confusion (21%). Treatments of neurologic AEs included tocilizumab (26%) and corticosteroids (38%). The median time to onset of neurologic AEs was 7 days (range, 1-32 days). The median duration of neurologic AEs was 12 days, with eventual resolution in 86% of patients (37/43). Patients with more robust expansion of KTE-X19 cells were more likely to experience high-grade cytokine-release

syndrome and neurologic events.

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Earlier Steroid Use With Axicabtagene Ciloleucel (Axi-Cel) in Patients With Relapsed/Refractory Large B-Cell Lymphoma

Axicabtagene ciloleucel is an autologous CAR T-cell therapy in which T cells from the patient are genetically modified to bind to CD19, thus enhancing the killing of cancer cells.¹ Common AEs from CAR T-cell therapy include cytokine-release syndrome and neurotoxicity, both of which require rigorous management. The phase 2 ZUMA-1 trial evaluated axicabtagene ciloleucel in patients with refractory large B-cell lymphoma.^{2,3} Cohort 1 included 77 patients with DLBCL, and cohort 2 included 24 patients with primary mediastinal B-cell lymphoma or transformed follicular lymphoma. Eligible patients had not responded to their most recent chemotherapy or had relapsed within 12 months after autologous SCT. Patients had an ECOG performance status of 0 or 1. After receipt of a conditioning regimen consisting of low-dose cyclophosphamide (500 mg/m²) and fludarabine (30 mg/m²) delivered on days -5, -4, and -3, patients received an infusion of 2 × 10⁶ CD19-directed CAR T cells per kilogram of body weight. Among 101 evaluable patients, the median follow-up was 27.1 months. The ORR was 83%, including a CR rate of 58%. After a median follow-up of 39.1 months, the median OS was 25.8 months and the 3-year OS rate was 47%. Cytokine-

release syndrome of grade 3 or higher was observed in 13% of patients, and neurologic events of grade 3 or higher occurred in 32%.

Two additional cohorts were added to evaluate management of cytokine-release syndrome and neurologic AEs.^{4,5} Patients in cohort 3 received prophylactic tocilizumab on day 2, which reduced the rate of severe cytokine-release syndrome to 3% (1/34), but did not reduce the incidence of severe neurologic AEs. An additional safety expansion cohort was therefore added to evaluate the

effect of earlier corticosteroid use on the rates of these AEs.⁴ Patients enrolled in cohort 4 had relapsed or refractory DLBCL, primary mediastinal B-cell lymphoma, transformed follicular lymphoma, or high-grade B-cell lymphoma. They had received at least 2 prior lines of therapy. After leukapheresis, patients were allowed to receive bridging therapy, including dexamethasone, high-dose methylprednisolone plus rituximab, or bendamustine plus rituximab. Following 3 days of conditioning with cyclophosphamide and fludarabine,

ABSTRACT SUMMARY Impact of Tisagenlecleucel Chimeric Antigen Receptor T-Cell Therapy Product Attributes on Clinical Outcomes in Adults With Relapsed or Refractory Diffuse Large B-Cell Lymphoma

The impact of key CAR T-cell attributes was evaluated in patients with relapsed or refractory DLBCL from the JULIET trial who received an infusion of tisagenlecleucel (Abstract 242). Tisagenlecleucel cell viability had no significant impact on 3-month response, duration of response, PFS, or OS, and no impact on rates of severe cytokine-release syndrome or neurologic AEs. The median T-cell transfusion efficiency also had no significant impact on efficacy or safety outcomes. Interferon-γ release ranged from 23.7 fg to 938 fg per CAR T cell. Durable responses were observed from CAR T-cell batches representing the entire range of interferon-γ release. Levels of interferon-γ release showed no correlation with the frequency or grade of cytokine-release syndrome or neurologic AEs. The median ratio of genetically modified CD4-positive cells to CD8-positive cells was 3.70 (range, 0.26-65.3). Efficacy or safety outcomes did not correspond to the ratio of CD4-positive cells to CD8-positive cells.

patients received a target dose of 2×10^6 CAR T cells/kg. Patients with grade 1 cytokine-release syndrome received tocilizumab and/or corticosteroid therapy if no improvement was observed after 3 days. Patients with grade 1 neurotoxicity received corticosteroid therapy, and tocilizumab was added for grade 2 or higher neurologic AEs.

Among the 41 patients in cohort 4 who received the axicabtagene ciloleucel infusion, 46% had stage IV disease. Their median age was 66 years (range, 19-77 years). Thirty-four percent of patients had undergone a prior SCT, 37% had disease progression after their most recent chemotherapy, and 20% had relapsed after autologous SCT.

CAR T-cell expansion was similar in cohorts 1 and 2 vs cohort 4 (Figure

5). In cohorts 1 and 2, the rate of grade 3 or higher cytokine-release syndrome was 13%. The rate was reduced to 2% in cohort 4. The rate of grade 3 or higher neurologic AEs decreased from 28% in cohorts 1 and 2 to 17% in cohort 4. No cases of grade 4 or 5 cytokine-release syndrome or neurologic AEs were observed in cohort 4. Compared with cohorts 1 and 2, the rates of cytokine-release syndrome and neurologic AEs of grade 3 or higher were reduced in cohort 4 for patients with a low or high tumor burden.

The mean cumulative corticosteroid dose was 13 ± 156 mg in cohorts 1 and 2 vs 5235 ± 76 mg in cohort 4. Peak levels of biomarkers including interferon- γ , interleukin-2, and C-reactive protein were lower in cohort 4 vs cohorts 1 and 2. In cohort 4, the ORR was 73%, with a CR

rate of 51%. The median duration of response was 8.87 months, and 54% of patients had an ongoing response at the time of the report (Figure 6).

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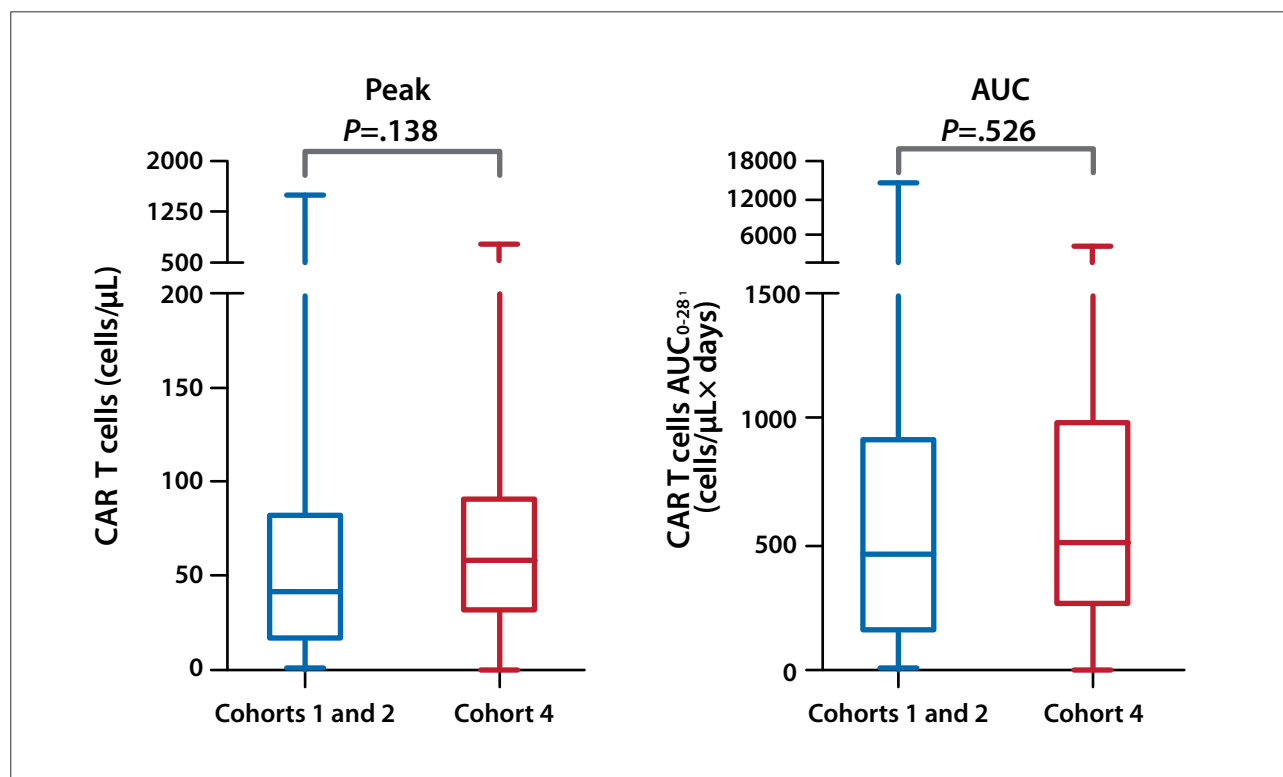


Figure 5. CAR T-cell expansion in the ZUMA-1 trial of axicabtagene ciloleucel in patients with relapsed/refractory large B-cell lymphoma. Patients in cohort 4 could receive bridging therapy, including dexamethasone, high-dose methylprednisone plus rituximab, or bendamustine plus rituximab. AUC, area under the curve; CAR, chimeric antigen receptor; ZUMA-1, Safety and Efficacy of KTE-C19 in Adults With Refractory Aggressive Non-Hodgkin Lymphoma. Adapted from Topp MS et al. ASH abstract 243. *Blood*. 2019;134(suppl 1).⁴

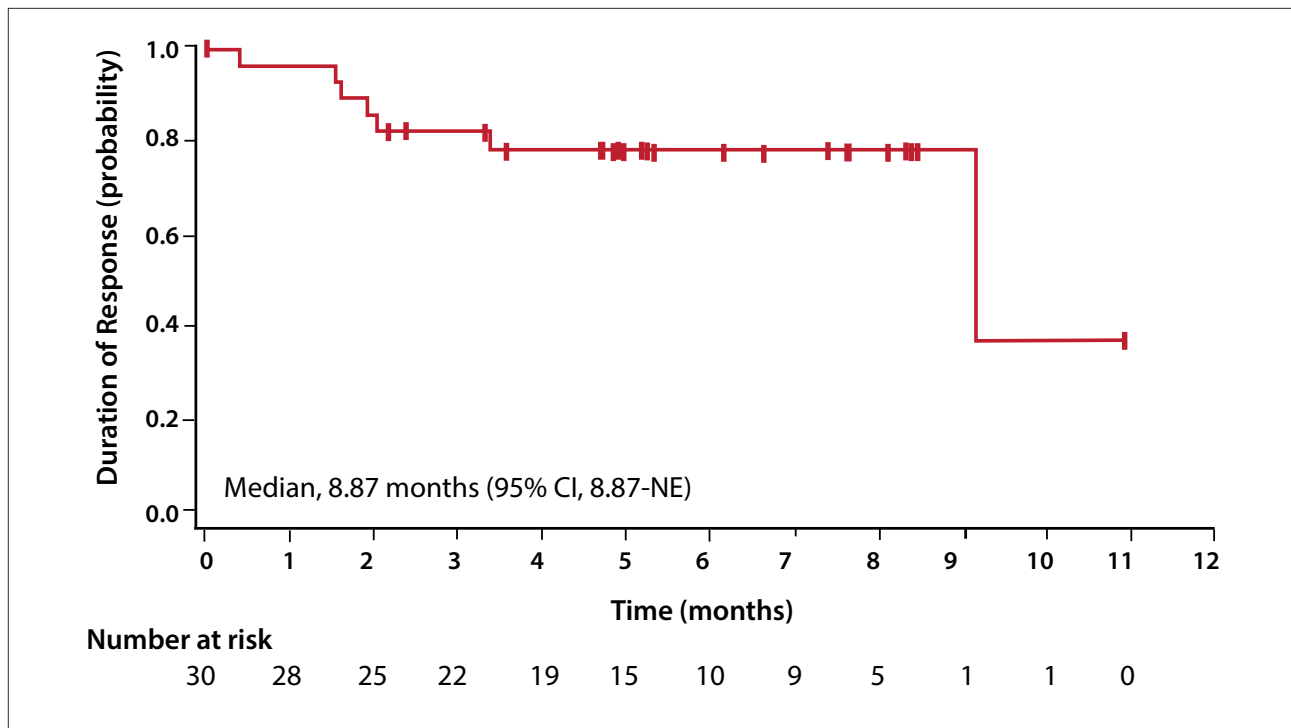


Figure 6. Duration of response among patients in cohort 4 of the ZUMA-1 trial of axicabtagene ciloleucel in patients with relapsed/refractory large B-cell lymphoma. Patients in this cohort could receive bridging therapy, including dexamethasone, high-dose methylprednisolone plus rituximab, or bendamustine plus rituximab. NE, not evaluable; ZUMA-1, Safety and Efficacy of KTE-C19 in Adults With Refractory Aggressive Non-Hodgkin Lymphoma. Adapted from Topp MS et al. ASH abstract 243. *Blood*. 2019;134(suppl 1).⁴

Characteristics and Outcomes of Patients Receiving Bridging Therapy While Awaiting Manufacture of Standard of Care Axicabtagene Ciloleucel CD19 Chimeric Antigen Receptor (CAR) T-Cell Therapy for Relapsed/Refractory Large B-Cell Lymphoma: Results From the US Lymphoma CAR-T Consortium

The US CAR-T Lymphoma Consortium evaluated real-world outcomes in patients with DLBCL, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma who received treatment with axicabtagene ciloleucel.^{1,2} The study identified 298 patients who underwent leukapheresis and 275 who received the axicabtagene ciloleucel infusion. Approximately half of patients (52%) were older than 60 years. ECOG performance status was 2 to 4 in 20%. The International Prognostic Index score was 3 to 5 in 54%. Twenty-three patients had triple-hit

genetics, 75% had received 3 or more prior lines of therapy, and 43% did not meet the inclusion criteria for the ZUMA-1 trial.

After a median follow-up of 13.8 months, the median PFS was 7.16 months. The median OS was not reached. Multivariate analysis showed a worse OS among patients who received bridging therapy vs those who did not (hazard ratio [HR], 1.8; 95% CI, 1.0-2.7; $P=.03$). Bridging therapy was used by 53% ($n=158$ patients). In contrast, bridging chemotherapy was used by no patients in the ZUMA-1 trial, 92% of those in the JULIET trial (Study of

Efficacy and Safety of CTL019 in Adult DLBCL Patients), and 59% of those in the TRANSCEND NHL 001 trial.³⁻⁵

Bridging therapy consisted of chemotherapy in 54%, only corticosteroids in 23%, radiation therapy in 12%, and targeted therapy in 10%. Patients who received bridging therapy were more likely to experience cytokine-release syndrome of at least grade 3 (9% vs 5% in those who did not), neurotoxicity of at least grade 3 (34% vs 28%), nonrelapse mortality (7.1% vs 1.5%), and death after lymphoma relapse (37% vs 17%). Among patients who underwent leukapheresis,

use of bridging therapy was also associated with a reduced median PFS (HR, 1.6; $P=.002$) and a reduced median OS (HR, 2.45; $P<.001$; Figure 7).

The efficacy of axicabtagene ciloleucel was similar among the 4 cohorts of different bridging strategies ($P>.05$). After propensity score matching, the P values ranged from 0.30 to 1.0. Outcomes were compared between the 104 patients without bridging therapy who were matched by propensity score to 104 patients who did receive bridging treatment. Among patients who under-

went leukapheresis, the median PFS was similar (HR, 1.2; $P=.3$). However, the median OS was superior in the cohort of patients who had not received bridging therapy (HR, 1.7; $P=.02$).

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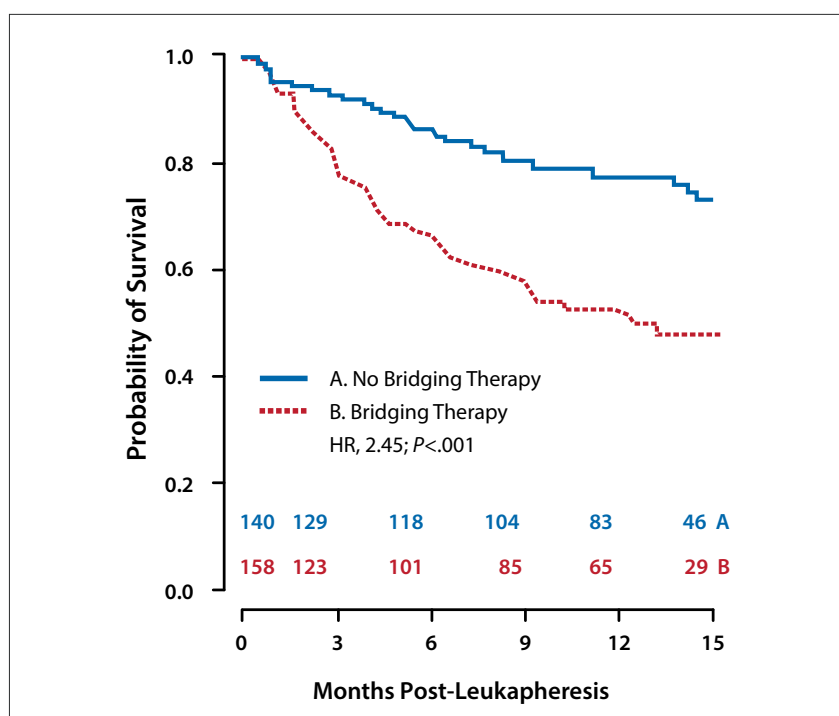


Figure 7. Overall survival was decreased among patients treated with bridging therapy in a real-world analysis of patients with diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma who received treatment with axicabtagene ciloleucel. HR, hazard ratio. Adapted from Jain MD et al. ASH abstract 245. *Blood*. 2019;134(suppl 1).¹

Real-World Data of High-Grade Lymphoma Patients Treated With CD19 CAR-T in England

In England, axicabtagene ciloleucel and tisagenlecleucel are currently available through the Cancer Drugs Fund, which provides interim funding for novel treatments until their clinical and cost-effectiveness can be determined.¹ Patients are approved to receive CAR T-cell therapy based on findings from a weekly meeting of the National

CAR-T Clinical Panel, which includes independent clinical experts, patient representatives, and delegates from 7 CAR T-cell treatment centers. The latter are located in geographically dispersed areas across England. The panel aims to use a transparent and objective approval process to provide equitable treatment access across regions, as well as to moni-

tor national capacity, assess outcomes and use of resources, and build expert competency. Eligibility criteria are similar to those for the ZUMA-1 and JULIET trials.^{2,3} Eligible patients have progressive disease based on Response Evaluation Criteria in Solid Tumors.⁴ A fresh biopsy is generally required for consideration of treatment.

The National Health Service England conducted a study to obtain real-world data on CAR T-cell therapy for the treatment of B-cell lymphoma.¹ The study enrolled 125 patients, of whom 116 underwent leukapheresis and 91 received a CAR T-cell infusion. Sixty-two patients received axicabtagene ciloleucel and 29 received tisagenlecleucel. The median time from approval to infusion was 63 days (range, 41-114 days). Lymphoma subtypes included de novo DLBCL (71%), transformed follicular lymphoma (18%), primary mediastinal B-cell lymphoma (6%), and transformed marginal zone lymphoma (5%). Seventy-six percent of patients had stage III/IV disease, and one-third had bulky disease (≥ 7.5 cm). Extranodal disease was present in 43% of patients, and 43% had received at least 3 prior lines of therapy. Bridging therapies included chemotherapy with or without corticosteroids (57%),

corticosteroids only (16%), and radiotherapy with or without corticosteroids (10%).

Among 56 patients who received treatment with axicabtagene ciloleucel, 21% had a CR and 16% had a partial response. Early progression occurred in 59% of patients, and 4% died. Among 24 patients who received a tisagenlecleucel infusion, 17% had a CR and 12% had a partial response. Early progression was noted in 71%. After a median follow-up of 7.0 months, the median OS was 9.1 months for the overall population of 124 evaluable patients (Figure 8). Among patients who were approved for CAR T-cell therapy, the median OS was not reached for those who did receive a CAR T-cell infusion (n=91) vs 2.3 months for patients who did not receive an infusion (n=33). The preliminary analysis suggests a lower rate of ongoing remissions compared with outcomes from pivotal clinical trials.^{2,3}

Cytokine-release syndrome of grade 3 or higher was observed in 11% of patients. Management consisted of tocilizumab in 65% and corticosteroids in 29%. Admission to an intensive care unit was needed by 34% of patients. Hematologic AEs of grade 3 or higher included neutropenia (19%) and thrombocytopenia (19%). Treatment-related mortality was 2%.

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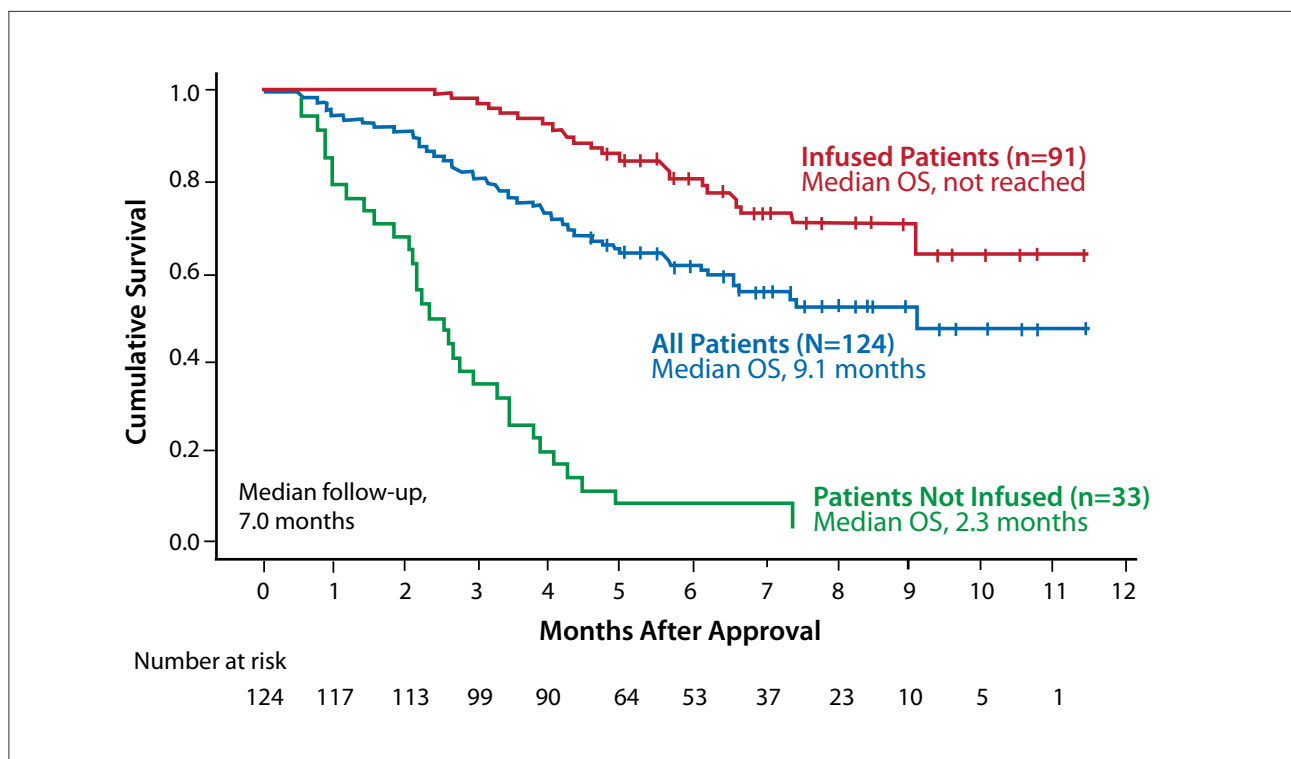


Figure 8. Overall survival among patients approved for CAR T-cell therapy in a real-world analysis from the National Health Service England. CAR, chimeric antigen receptor. Adapted from Kuhn A et al. ASH abstract 767. *Blood*. 2019;134(suppl 1).¹

Post-Marketing Use Outcomes of an Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy, Axicabtagene Ciloleucel, for the Treatment of Large B-Cell Lymphoma in the United States

An ongoing study in the United States is using the infrastructure created by the Center for International Blood and Marrow Transplant Research (CIBMTR) to evaluate the real-world safety and efficacy of axicabtagene ciloleucel.¹ The study includes patients who received axicabtagene ciloleucel and agreed to share their data with the CIBMTR. Follow-up will last for 15 years as part of a postmarketing regulatory requirement. The study has a planned accrual of 1500 large B-cell lymphoma patients. The objectives are to describe early safety and efficacy outcomes and to analyze treatment patterns based on age. The study included patients with large B-cell lymphoma who received commercial axicabtagene ciloleucel after approval by the US Food and Drug Administration.

Among 750 enrolled patients, 533 attended a first follow-up appointment. Most of these patients (63%) were younger than 65 years. There were 326 patients with at least 6 months of follow-up, and 218 were younger than 65 years.

Among the 533 patients who attended a first follow-up appointment, the median age was 61 years (range, 19-86 years), and 66% were male. The ECOG performance status was 0 or 1 in 80% of patients and 2 or higher in 4%. (The score was unknown in 15%.) The disease was transformed lymphoma in 30%, double- or triple-hit lymphoma in 36%, and chemotherapy-resistant in 62%. Thirty-two percent of patients had received a prior autologous SCT. The median time from diagnosis to axicabtagene ciloleucel infusion was 16 months. Compared with patients in

the ZUMA-1 trial,² those in the current study were older (median age, 61 vs 58 years), were more likely to have high-risk genetics (36% vs 11%), and were more likely to have undergone autologous SCT (32% vs 25%).

The ORR was 74% among the 533 patients who attended a first follow-up appointment. ORR was 79% in patients ages 65 years or older vs 71% in younger patients ($P=.07$). The 326 patients with at least 6 months of follow-up had an ORR of 84% (Figure 9). ORR was 92% in older patients vs 80% in younger patients ($P=.02$). The median duration of response was similar for both older and younger patients ($P=.170$), as were the median PFS ($P=.059$) and median OS ($P=.618$).

Cytokine-release syndrome of any-grade occurred in 80% of younger patients vs 84% of older patients.

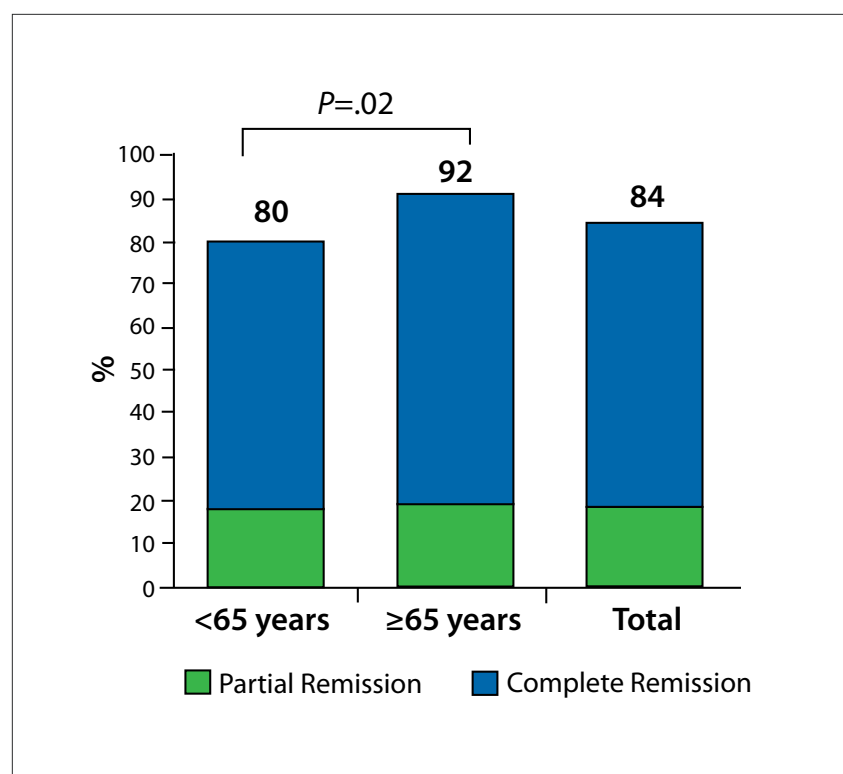


Figure 9. Overall response among patients with at least 6 months of follow-up treated with axicabtagene ciloleucel in a real-world analysis. Adapted from Pasquini MC et al. ASH abstract 764. *Blood*. 2019;134 (suppl 1).¹

Rates of high-grade cytokine-release syndrome were 8% vs 10%, respectively. In both age groups, the median time to cytokine-release syndrome was 3 days, and the median duration was 7 days. Cytokine-release syndrome resolved in 94% of patients younger than 65 years and in 93% of patients ages 65 years and older. The rate of

grade 3 or higher neurologic toxicity was 19% in younger patients vs 22% in older patients. Neurotoxicity resolved in 89% vs 87%, respectively. The median time to onset was 6 days for both cohorts. The median duration of neurotoxicity was 7 vs 10 days. Rates of subsequent neoplasms were similar for both age groups.

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Tisagenlecleucel Chimeric Antigen Receptor T-Cell Therapy for Adults With Diffuse Large B-Cell Lymphoma: Real World Experience From the Center for International Blood & Marrow Transplant Research Cellular Therapy Registry

A registry to track long-term outcomes among patients treated with CAR T-cell therapy was initiated in September 2018.¹ The registry will follow 2500 patients with lymphoma, including 1000 with acute lymphoblastic leukemia, for 15 years. Cohorts will be analyzed based on forms of infusion, safety, efficacy, and CAR T-cell manufacturing. An initial cohort of 116 patients with non-Hodgkin lymphoma received the tisagenlecleucel infusion. Patients were a median age of 65 years (range, 15-89 years). Double- or triple-hit genetics was reported in 41%, and 27% had transformed lymphoma. Thirty-two percent had refractory disease, and 28% had received prior SCT.

The median time from diagnosis to administration of CAR T-cell therapy was 15 months, and the median time from the start of manufacturing to CAR T-cell infusion was 32 days. The median number of viable CAR T cells was 1.7×10^8 (range, 0.4×10^8 to 6.8×10^8). Most patients (89%) received cyclophosphamide plus fludarabine for lymphodepletion.

After a median follow-up of 4.5 months, the ORR was 58%, with a 40% CR rate. The 3-month duration of response was 75.2%. Three-month PFS was 61.6%, and 3-month OS was 79.6%.

Forty-nine percent of patients developed any-grade cytokine-release syndrome. Grade 4 cytokine-release syndrome occurred in 1%, and grade 5 cases occurred in 2%. The median time to onset of cytokine-release syndrome was 4 days (range, 2-14 days), and the median duration was 5 days (range, 4-8 days).

Any-grade neurotoxicity occurred in 16% of patients. Grade 3, 4, and 5

neurologic AEs were observed in 1%, 4%, and 1% of patients, respectively. The median time to onset of neurologic AEs was 8 days (range, 2-27 days), and the median duration was 14 days (range, 5-25 days).

Efficacy and safety outcomes were similar for CAR T-cell preparations that had between 60% and 79% viable CAR T cells and those with a viability

ABSTRACT SUMMARY Detectable Circulating Tumor DNA 28 Days After the CD19 CAR T-Cell Therapy, Axicabtagene Ciloleucel, Is Associated With Poor Outcomes in Patients With Diffuse Large B-Cell Lymphoma

Among patients treated with CAR T-cell therapies, early identification of increased risk of relapse may permit early intervention to improve outcomes. A multi-institutional, prospective study used cell-free minimal residual disease (MRD) assessment to predict outcomes in patients with relapsed/refractory DLBCL who received axicabtagene ciloleucel (Abstract 884). The analysis included 64 patients. High levels of circulating tumor DNA before lymphodepletion were associated with poor outcomes, including lower PFS. The average level of plasma cell circulating tumor DNA before lymphodepletion was 15-fold higher in patients who developed progressive disease. The average level of plasma cell circulating tumor DNA began to rise on day 28 among patients with progressive disease. Patients who were MRD positive on day 28 had poor clinical outcomes. The median PFS was 3.0 months among MRD-positive patients vs not reached among MRD-negative patients ($P < .001$). Detection of MRD predicted relapse. Day 28 assessment of MRD using circulating tumor DNA compared favorably with assessments using positron emission tomography/computed tomography. The investigators concluded that the results provide a rationale for designing risk-adapted clinical trials in CAR T-cell therapy that incorporate measurement of circulating tumor DNA.

of at least 80% of cells (Figure 10). The ORR was 54% in patients who received the lower viability preparation vs 59% for those who received the higher viability preparation. The 3-month duration of response was 70% vs 79%, respectively, and 3-month OS was 75% vs 84%. Any-grade cytokine-release syndrome rates were 38% vs 49%, and rates of any-grade neurotoxicity were 13% vs 17%. The ORR was numerically lower among patients infused with preparations in the lowest quartile of viable CAR T cells, but the difference was not significant. All of the grade 3 to 5 cytokine-release syndrome events occurred in patients who received CAR T-cell preparations in viability quartile 3 ($1.69\text{-}2.26 \times 10^8$ cells).

The CIBMTR registry and the JULIET trial provided similar outcome data, including for ORR (58% vs 52%) and CR rate (40% vs 38%).² Rates of high-grade cytokine-release syndrome were lower in the CIBMTR registry (4% vs 23%), as were rates of high-grade neu-

rotoxicity (5% vs 11%). However, the 2 trials used different grading guidelines for cytokine-release syndrome.

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ABSTRACT SUMMARY Experience With Axicabtagene Ciloleucel in Patients With Secondary CNS Involvement: Results From the US Lymphoma CART Consortium

A real-world, retrospective study evaluated outcomes in patients with secondary CNS involvement who received an axicabtagene ciloleucel infusion at 1 of 17 academic centers associated with the US CAR-T Lymphoma Consortium (Abstract 763). Thirteen patients had a history of CNS involvement, and 8 patients had active CNS involvement at the time of the axicabtagene ciloleucel infusion. Baseline demographics were similar for patients with or without CNS involvement. The ORR at 6 months was 48% for the 257 patients without CNS involvement, 44% for the 18 patients with CNS involvement, 50% for the 8 patients with active CNS involvement at the time of the axicabtagene ciloleucel infusion, and 40% for the 10 patients with a history of CNS involvement. Rates of event-free survival were similar for patients with vs without CNS involvement, as determined from the time of leukapheresis ($P=.14$) and from the time of the axicabtagene ciloleucel infusion ($P=.24$).

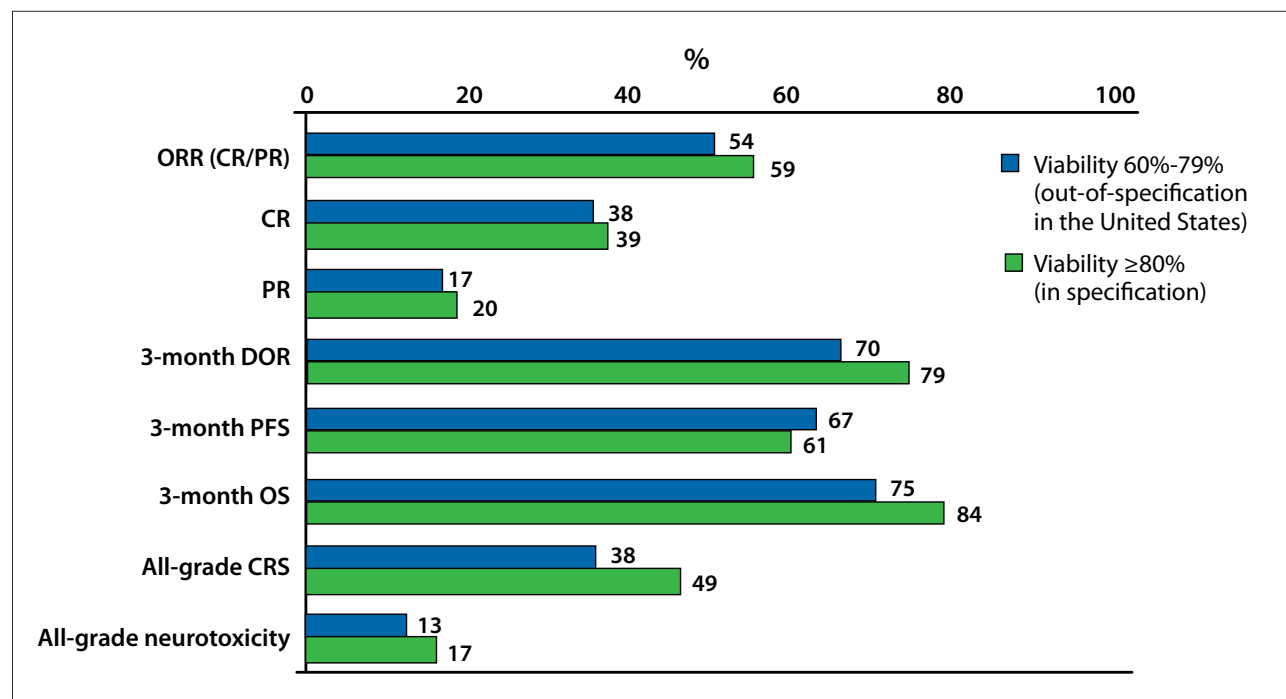


Figure 10. Cell viability did not impact safety or outcome in a real-world analysis of patients with diffuse large B-cell lymphoma treated with tisagenlecleucel. CR, complete response; CRS, cytokine-release syndrome; DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival. Adapted from Jaglowski S et al. ASH abstract 766. *Blood*. 2019;134(suppl 1).¹

Highlights in CAR T-Cell Therapy From the 61st American Society of Hematology Annual Meeting: Commentary

Caron A. Jacobson, MD

Several studies in chimeric antigen receptor (CAR) T-cell therapy presented at the 61st American Society of Hematology (ASH) meeting provided important insights into the use of this treatment. Results from clinical trials were presented for lisocabtagene maraleucel and KTE-X19. Follow-up analyses and real-world reports examined data for axicabtagene ciloleucel and tisagenlecleucel.

Clinical Trial Data

Dr Jeremy S. Abramson and colleagues presented results of the TRANSCEND NHL 001 trial,¹ the third pivotal study of a CD19-directed CAR T-cell product. The study evaluated lisocabtagene maraleucel in patients with relapsed/refractory large B-cell lymphoma. Lisocabtagene maraleucel is a 4-1BB CAR product, like tisagenlecleucel. A unique aspect to lisocabtagene maraleucel is that it is formulated in a 1:1 ratio of CD4 to CD8 T cells. TRANSCEND started as a nonpivotal registrational study. It originally had different eligibility criteria compared with previous registrational studies, but was later modified to include a core cohort that would be used for registration purposes. Data were presented at the ASH meeting.¹ The study evaluated different doses and numbers of infusions in a dose-finding portion. However, the study treated a majority of patients (n=126) at the confirmed recommended phase 2 dose in a single infusion. A key point of the study concerns the broad population. It not only included the largest cohort of patients treated with aggressive B-cell non-Hodgkin lymphoma among the pivotal studies,^{2,3} it also included patients who would have been excluded from the other studies, including those with an Eastern Cooperative Oncology Group performance status of 2, those with secondary central nervous system

lymphoma, those who had undergone a prior allogeneic transplant, those with a creatinine clearance between 30 and 60 mL/min, and those with a cardiac ejection fraction between 40% and 50%.

The number of patients who had their cells collected was 344, but the number of patients included in the efficacy analysis was only 256. There are several reasons for this drop-off. Thirty-three patients died after undergoing leukapheresis and before receiving the infusion. An additional 17 patients underwent leukapheresis but did not receive the infusion, 6 owing to disease-related complications. The CAR T-cell product could not be manufactured for 2 patients. Twenty-five patients were excluded from the efficacy analysis because the CAR T-cell product did not meet the protocol specifications for infusion. These patients still received the infusion, but under a protocol such as the single-patient Investigational New Drug program. Lastly, 13 patients were treated but not evaluable because they had a complete response to bridging therapy or they had not undergone positron-emission tomography (PET). The PET scan was required to measure their response to bridging therapy and to establish a new baseline scan against which to judge their response to lisocabtagene maraleucel.

The overall response rate (ORR) was based on a modified intention-to-treat analysis that included only the patients who received lisocabtagene maraleucel. The rate will decrease if the analysis included all patients who underwent leukapheresis. With CAR T-cell therapy, the efficacy and safety of an individual product are certainly important concerns, but so is the proportion of patients who will be able to receive the product after leukapheresis.

Dr Abramson presented the safety data first.¹ Lisocabtagene maraleucel is

potentially safer than the 2 CAR T-cell products approved in this space, axicabtagene ciloleucel and tisagenlecleucel, based on the data from clinical trials.^{2,3} The rate of grade 3 or higher cytokine-release syndrome (CRS) was 2%, and the median time to onset of CRS was 5 days. Therefore, fewer patients required admission to the intensive care unit after developing CRS. CRS typically arises 5 days after infusion, raising the potential for administration in the outpatient setting, where patients can be monitored and then hospitalized only if needed. Any-grade cytokine release syndrome occurred in 42% of patients, indicating that many patients can avoid hospitalization. Neurologic toxicity of grade 3 or higher occurred in 10% of patients, which is a fairly low number. Any-grade neurologic toxicity was reported in 30% of patients.

Hospitalization in the intensive care unit was required by 7% of patients, despite the lower incidence of grade 3 or higher CRS. This observation underscores the data showing that these therapies have considerable high-grade toxicity and risk, and that patients treated with them require access to a medical center that can deliver high-quality, specialized management in an intensive care unit.

With respect to efficacy, the rates of overall response and complete response were similar to those seen with the other T-cell products.^{2,3} The complete response rate was 53%, and the ORR was 73%. The responses were durable, persisting at 6 and 12 months; in a Kaplan-Meier graph, the curve for the duration of response appeared to plateau around that time. The presence of high-risk disease characteristics did not impact response. However, other clinical trials and analyses suggest that patients with a higher disease burden are less likely to have a complete

response after CAR T-cell therapy.^{2,4,5}

The TRANSCEND trial provided efficacy data according to disease histology. This study is the first in CAR T-cell therapy to show a separate response rate for patients with primary mediastinal large B-cell lymphoma. These patients, along with patients with transformed follicular lymphoma, did better than patients with high-grade B-cell lymphoma, diffuse large B-cell lymphoma, and other transformed indolent lymphomas.

There has been a question regarding the long-term benefits of bridging therapy given between T-cell collection and T-cell infusion on efficacy as well as toxicity. The pivotal trials had different allowances for bridging therapy. In the TRANSCEND trial, the use of bridging therapy did not impact outcome.¹ As mentioned, the TRANSCEND trial had a broader eligibility criteria than previous studies, enrolling patients with high-risk characteristics, such as comorbidities involving cardiac or renal function, patients who had undergone allogeneic transplant, and patients with central nervous system disease. An analysis suggested that patients without comorbidities had a better outcome than patients with comorbidities, which is an important new observation. Patients with comorbidities still did better after CAR T-cell therapy than they would have with other available therapies; this finding highlights that these patients still benefit from this treatment, although they represent an unmet medical need and require more effective and safer cellular therapy options.

This study demonstrates that lisocabtagene maraleucel is a highly active CAR T-cell therapy with a potentially safer toxicity profile that could allow administration in the outpatient setting. In the clinic, it will be important to see how many patients can receive treatment after leukapheresis. If manufacturing is efficient and patients are able to receive treatment, then lisocabtagene maraleucel will be an important addition to this field once it

is approved by the US Food and Drug Administration (FDA).

Dr Michael Wang and colleagues presented a study of KTE-X19 in patients with mantle cell lymphoma.⁶ This study is the first in CAR T-cell therapy to enroll a large series of patients with mantle cell lymphoma. KTE-X19 is similar to axicabtagene ciloleucel in all attributes except for one. The manufacturing process of KTE-X19 selects out T cells from potential leukemia or lymphoma cells, thereby removing the circulating tumor cells before expansion and activation. The study enrolled patients with fairly high-risk disease. Patients had received previous treatment with chemoimmunotherapy and a Bruton tyrosine kinase (BTK) inhibitor. Their expected survival was short. Between leukapheresis and infusion, patients could receive bridging therapy with either corticosteroids or a BTK inhibitor. The median time from leukapheresis to delivery of KTE-X19 was 16 days.

The product was successfully manufactured for 96% of patients and administered to 92% of patients. These data are similar to those in the ZUMA-1 trial.² Approximately 17% of patients had a *TP53* mutation, 70% had a high Ki-67, and more than 30% had blastoid or pleomorphic morphology. All of these characteristics predict for inferior outcomes with conventional therapies.

The trial showed an impressive ORR of 93%, including a complete response rate of 67%. The median follow-up was approximately 12 months. Approximately 47% of patients had at least 2 years of follow-up, and responses were durable. It is necessary to have a longer follow-up in mantle cell lymphoma compared with large cell lymphoma to hypothesize whether a therapy might offer a potential cure. The results of this study, though, are promising. At 12 months, 57% of patients were still in response. Among patients with a complete response, this response was maintained in 78%.

The side effect profile was similar to that of axicabtagene ciloleucel in large cell lymphoma. Grade 3 or higher CRS occurred in 15% of patients. The median time to onset was 2 days. The rate of grade 3 or higher neurologic toxicity was 31%. It appeared that patients with better CAR T-cell expansion were more likely to respond and to achieve minimal residual disease (MRD) negativity. However, increased production of CARs corresponds with high-grade toxicity.

This study is the first to show that a CAR T-cell therapy can achieve an impressive response rate and good durability of response in a high-risk, refractory population of patients with mantle cell lymphoma. This treatment has the potential to change the natural history of the disease for many patients. These data will likely lead to approval from the FDA.

Follow-Up Analysis

Dr Sattva S. Neelapu and colleagues evaluated rates of CD19 loss in a small cohort of patients who received axicabtagene ciloleucel.⁷ The study documented a reasonably high rate of CD19 loss. Before treatment, 90% of patients were CD19-positive. This rate dropped to 72% after treatment among the samples evaluated by immunohistochemistry. There seemed to be a selection for tumor cells that had lower CD19 antigen expression. The study also identified patients who had alternative splicing of CD19 that led to a loss of the epitope that the CAR binds to. Importantly, the study showed that nearly all of the patients who lost CD19 still retained other B-cell antigens. This study not only documented the rates of CD19 loss in large cell lymphoma after axicabtagene ciloleucel, but also provided rationale for studying dual-antigen CARs that target more than one B-cell antigen simultaneously. Ongoing phase 2 multicenter clinical trials are evaluating this presently, with results expected in the next few years.^{8,9}

Real-World Reports

There were several real-world reports, some drawn from the Center for International Blood & Marrow Transplant Research (CIBMTR) database. A study by Dr Samantha Jaglowski evaluated real-world use of tisagenlecleucel in 80 patients.¹⁰ Rates of overall response and complete response were similar to those in clinical trials. The follow-up is short at this time. However, between 60% and 70% of patients appear to maintain their response at the 3-month mark, which is predictive of durable remissions in clinical trials.^{2,3}

The JULIET study of tisagenlecleucel used a different grading scale for CRS than the other trials, and the rate of grade 3 or higher events was 22%.³ In the real-world analysis, 80 patients were evaluated for CRS based on the standardized scale set forth by the American Society for Transplantation and Cellular Therapy.¹¹ The rate of grade 3 or higher cytokine release syndrome was only 3%, which is similar to the rate in the TRANSCEND study, which evaluated lisocabtagene maraleucel, the other 4-1BB CAR.¹ The improved rates of CRS may reflect both the use of a modern toxicity grading scale as well as improvements in treating and managing CRS. Rates of grade 3 or higher neurologic toxicity, as assessed using an updated consensus scale, were also lower in the real-world study vs the JULIET trial. These rates were 6% in the real-world series vs 12% in the JULIET study.³ Again, this may reflect improvements in toxicity management and treatment. In this real-world study, efficacy was similar to that in the JULIET clinical trial, but safety was improved.

Dr Marcelo Pasquini presented data from the CIBMTR for 533 patients treated with axicabtagene ciloleucel.¹² Efficacy is similar to that in clinical trials, with an ORR of 70% to 80%, and a complete response rate of approximately 50%. After at least 6 months of follow-up, a complete response persisted in most patients.

This analysis evaluated data according to age to allay concerns that this is a therapy that should be limited to younger patients. Interestingly, in older patients, the response rates were higher, and responses were more durable.

In the real-world analysis, grade 3 or higher CRS occurred in less than 10% of patients, which is lower than in the ZUMA-1 trial.² This decrease likely reflects improvements in management. However, only approximately 15% of patients did not have CRS. The rate of grade 3 or higher neurologic toxicity was approximately 20%, which is also better than that seen in the ZUMA-1 trial,² but higher than that seen with lisocabtagene maraleucel or tisagenlecleucel.^{1,3} Neurologic toxicity was not increased in patients who were older than 65 years. This real-world analysis supports the use of axicabtagene ciloleucel in the older population.

Dr Michael D. Jain and colleagues from the US CAR T-cell consortium evaluated bridging therapy in a real-world cohort of patients treated with axicabtagene ciloleucel. Bridging therapy was used by 53% of patients.¹³ Bridging therapy consisted of chemotherapy in 54%, corticosteroids in 23%, radiation in 12%, and targeted agents in 10%. Patients who received bridging therapy had several poor-risk characteristics. They were more likely to have a poor performance status, advanced-stage disease, a high International Prognostic Index, and bulky disease. These patients probably had worse disease, were sicker at baseline, and were less likely to respond in general.

There was no difference in the rates of CRS and neurotoxicity in the groups that did or did not receive bridging therapy. However, the rate of nonrelapse mortality and death (presumably related to treatment) was 7.1% in patients who received bridging therapy and 1.5% in patients who did not. There was also a higher rate of death related to lymphoma relapse, at 37% vs 17%, respectively. Patients who received bridging therapy had

decreased progression-free survival and overall survival. When using a propensity score matching analysis to control for factors associated with worse outcomes, bridging therapy remained an independent predictive factor for inferior overall survival. Patients treated with CAR T cells after bridging therapy still have better outcomes than patients treated with the current standard of care, but like the patients with comorbidities in the TRANSCEND study, they represent an unmet need.

This study also used a propensity score matching analysis to control for factors that predict for higher-risk disease. The worse rates of progression-free survival and overall survival seen in patients who received bridging therapy persisted in this analysis. All types of bridging therapies were associated with the worse outcome.

Like the TRANSCEND trial, this analysis showed that outcome is inferior among patients with comorbidities and who undergo bridging therapy.¹ Patients treated with CAR T cells after bridging therapy still have better outcomes than patients treated with the current standard of care, but they represent an unmet need.

An analysis of real-world data from England of patients treated with CAR T-cell therapy found that toxicity was better but efficacy was worse as compared with data from clinical trials.^{2,3,14} In England, the mechanism for identifying and approving therapy for an individual patient involves a comprehensive central review process. Patients are selected for treatment with CAR T-cell therapy only if they are in good physical condition. Selected patients must wait much longer to receive treatment compared with patients in the United States. It may be that the decreased efficacy in this analysis reflects this delay, by allowing the disease to progress.

DNA Levels and Response

CAR T-cell therapy is associated with high response rates, but also significant relapse rates. It appears that approxi-

mately 40% of patients will achieve long-term remissions.^{2,3} There is interest in trying to identify patients who may potentially relapse in order to administer interventions that could manipulate CAR T cells or other functional T cells to continue to fight against the residual lymphoma. Two abstracts presented at the ASH meeting evaluated MRD after use of axicabtagene ciloleucel in a commercial setting. A study presented by Dr Matthew J. Frank included a cohort of 64 patients.⁴ These patients had the same outcomes as were seen in the ZUMA-1 trial. The study followed MRD levels serially through month 12. The investigators assessed circulating tumor DNA sequences of the mutated immunoglobulin heavy chain (*IgH*) gene for patient-specific lymphoma. For this assessment, it is necessary to sequence *IgH* from an original tumor biopsy and then measure it in the blood at serial time points. Patients who had a high level of this gene before treatment were less likely to respond. The analysis by Dr Frank showed that patients who are MRD-negative at day 28—the typical time of the first PET assessment—were much more likely to maintain a response and had better progression-free survival and overall survival compared with patients who were MRD-positive.⁴ MRD negativity at this time was slightly superior to positron emission tomography in predicting improved long-term outcome.

A study presented by Dr Brian Sworder used a slightly different technology known as cancer personalized profiling by deep sequencing (CAPP-Seq), which measures circulating tumor DNA by identifying DNA sequences for a prespecified set of highly mutated genes in large cell lymphoma.⁵ As with the previous study, this analysis showed that higher pretreatment circulating tumor DNA levels correlated with increased tumor burden and a lower likelihood of a durable response. Outcome was worse in patients with detectable circulating tumor DNA at day 28. An interesting aspect about this

technology is that the sequence for the actual CAR can be incorporated into the panel, and the CAR T cells can be tracked over time to measure expansion and persistence. The study showed that CAR T-cell expansion did not correlate with outcome. The investigators evaluated the mutational burden in patients before treatment. Patients who developed progressive disease had a different disease mutation profile from those who did not. These data are preliminary, but they suggest how this technology might be used to predict response.

A study presented by Dr Veronika Bachanova and colleagues evaluated 115 tisagenlecleucel products to explore two questions.¹⁵ The first concerned viability. The FDA has set a viability for tisagenlecleucel to be in specification of 80%,^{16,17} although patients in the clinical trial had a T-cell viability of 70% or higher.³ The analysis by Dr Bachanova showed that there was no difference in outcomes for patients who had cells that were 70% viable vs 80% viable. In the real world, patients who have a T-cell viability of less than 80% receive treatment under an expanded access protocol and not under commercial settings. However, this analysis supports expansion of the FDA label to encompass T-cell viability of 70% or greater. The analysis also examined the CD4 to CD8 T-cell composition of the product that was infused into the patients. There was no ratio that predicted for improved or decreased efficacy. However, patients who received a product with a higher proportion of CD4 CAR T cells had increased rates of grade 3 or higher CRS.

Disclosure

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