

A SPECIAL MEETING REVIEW EDITION

**Advances in Aggressive Lymphoma From the 2017
American Society of Hematology Annual Meeting and
Exposition**

A Review of Selected Presentations From the 2017 American Society of Hematology
Annual Meeting and Exposition • December 9-12, 2017 • Atlanta, Georgia

Special Reporting on:

- Long-Term Follow-Up of ZUMA-1: A Pivotal Trial of Axicabtagene Ciloleucel (Axi-Cel; KTE-C19) in Patients With Refractory Aggressive Non-Hodgkin Lymphoma
- Primary Analysis of JULIET: A Global, Pivotal, Phase 2 Trial of CTL019 in Adult Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma
- A Comparison of One Year Outcomes in ZUMA-1 (Axicabtagene Ciloleucel) and SCHOLAR-1 in Patients With Refractory, Aggressive Non-Hodgkin Lymphoma
- High Durable CR Rates in Relapsed/Refractory (R/R) Aggressive B-NHL Treated With the CD19-Directed CAR T Cell Product JCAR017 (TRANSCEND NHL 001): Defined Composition Allows for Dose-Finding and Definition of Pivotal Cohort
- Phase 1 Results From ZUMA-6: Axicabtagene Ciloleucel (axi-cel; KTE-C19) in Combination With Atezolizumab for the Treatment of Patients With Refractory Diffuse Large B-Cell Lymphoma
- Effect of Rituximab in Primary Central Nervous System Lymphoma—Results of the Randomized Phase III HOVON 105/ALLG NHL 24 Study
- Encouraging Early Results From the First in-Human Clinical Trial of ADCT-402 (Loncastuximab Tesirine), a Novel Pyrrolbenzodiazepine-Based Antibody Drug Conjugate, in Relapsed/Refractory B-Cell Lineage Non-Hodgkin Lymphoma

PLUS Meeting Abstract Summaries

With Expert Commentary by:

Frederick L. Locke, MD

Vice Chair and Associate Member

Department of Blood and Marrow Transplant and Cellular Immunotherapy

Moffitt Cancer Center

Tampa, Florida

ON THE WEB:
hematologyandoncology.net

NOW APPROVED



YESCARTA™

(axicabtagene ciloleucel) Suspension
for IV infusion

INTRODUCING A NEW CAR T THERAPY

Find a list of authorized treatment centers
at YESCARTA.com/centers

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

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)].

Important Safety Information continued on adjacent page.

IMPORTANT SAFETY INFORMATION (continued)

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)].

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*].

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).

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™.

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 antimicrobials 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.

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.

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™.

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.

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.

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥ 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 (≥ 10%) Grade 3 or higher reactions include febrile neutropenia, fever, CRS, encephalopathy, infections-pathogen unspecified, hypotension, hypoxia, and lung infections.

Please see Brief Summary of Prescribing Information, including **BOXED WARNING**, on adjacent pages.

BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR YESCARTA™
(axicabtagene ciloleucel) 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). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. 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 (%)
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)].

Manufactured by, Packed by, Distributed by: Kite Pharma, Inc., Santa Monica, CA 90404
US License No 2064

YESCARTA is a trademark of Kite Pharma.

© 2017 Kite Pharma | PRC-00159 11/2017

Long-Term Follow-Up of ZUMA-1: A Pivotal Trial of Axicabtagene Ciloleucel (Axi-Cel; KTE-C19) in Patients With Refractory Aggressive Non-Hodgkin Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL). Up to half of these patients relapse after treatment or develop refractory disease.¹ Treatment of patients with relapsed or refractory disease continues to present a challenge. A recent retrospective multicohort study of more than 600 patients with refractory DLBCL showed an objective response rate (ORR) of 26%, a complete response (CR) rate of 7%, and a median overall survival (OS) of 6.3 months after treatment with salvage chemotherapy.² Chimeric antigen receptor (CAR) T-cell therapy is a novel treatment modality for patients with relapsed or refractory NHL. Axicabtagene ciloleucel is an autologous

anti-CD19 CAR T-cell therapy that was approved in October 2017 by the US Food and Drug Administration for the treatment of adults with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy.^{3,4} The treatment consists of autologous peripheral blood T cells that have been transduced with a gammaretroviral vector that confers expression of the CAR. The CAR consists of an anti-CD19 single-chain variable fragment (Fv) plus the costimulatory signaling domains CD28 and CD3 zeta. After the engineered T cell engages with a CD19-expressing target cell, the costimulatory domains activate downstream signaling cascades that lead to T-cell activation, proliferation, acquisition of effector functions, and

secretion of inflammatory molecules, resulting in target cell death. ZUMA-1 (A Phase 1-2 Multi-Center Study Evaluating Axicabtagene Ciloleucel in Subjects With Refractory Aggressive Non-Hodgkin Lymphoma) was a phase 1/2 trial that evaluated axicabtagene ciloleucel in patients with refractory DLBCL, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma.⁵ Eligible patients had not responded to their most recent chemotherapy or had relapsed within 12 months of undergoing autologous stem cell transplant. Seven patients were treated in a single cohort in the phase 1 trial. The phase 2 portion of the trial included 101 patients: 77 with refractory DLBCL and 24 with refractory primary mediastinal B-cell

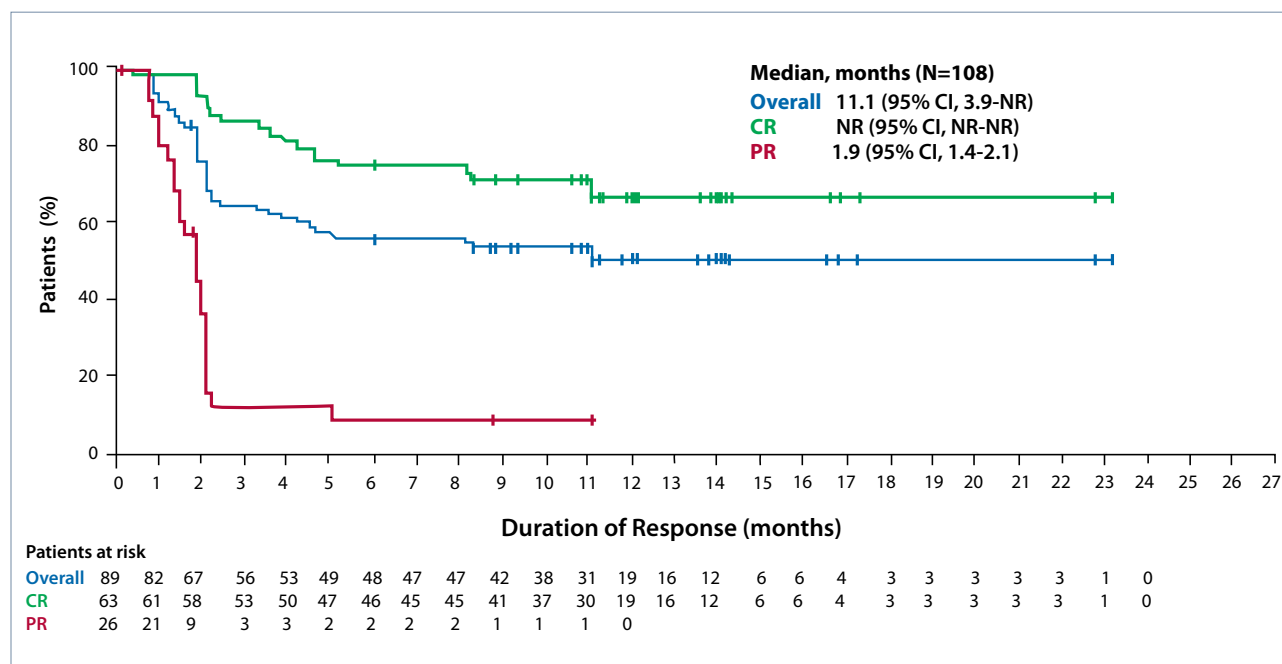


Figure 1. Duration of response according to best objective response in long-term follow-up of the ZUMA-1 trial, which evaluated axicabtagene ciloleucel in refractory aggressive non-Hodgkin lymphoma. CR, complete response; NR, not reached; PR, partial response. Adapted from Neelapu SS et al. ASH abstract 578. *Blood*. 2017;130(suppl 1).⁶

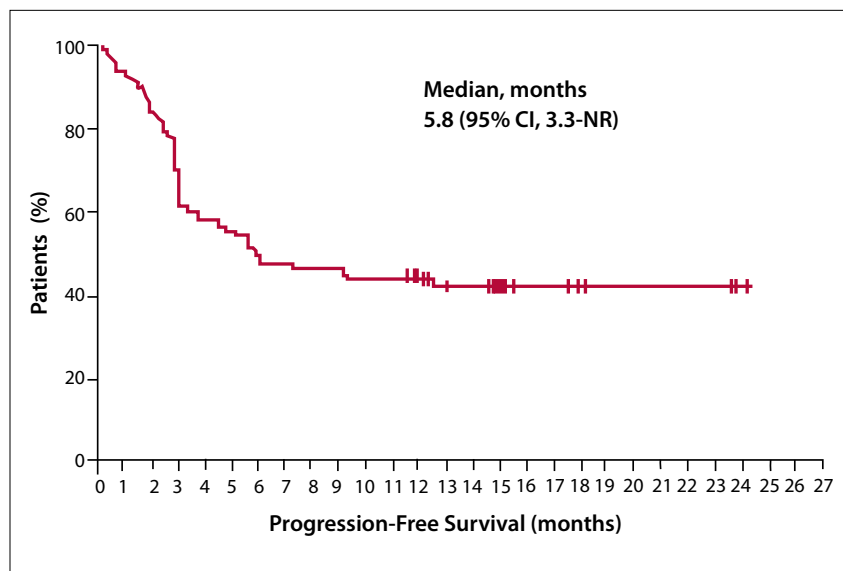


Figure 2. Long-term analysis of progression-free survival in the ZUMA-1 trial of axicabtagene ciloleucel in refractory aggressive non-Hodgkin lymphoma. NR, not reached. Adapted from Neelapu SS et al. ASH abstract 578. *Blood*. 2017;130(suppl 1).⁶

ABSTRACT SUMMARY Preliminary Results of Prophylactic Tocilizumab After Axicabtagene Ciloleucel (axi-cel; KTE-C19) Treatment for Patients With Refractory, Aggressive Non-Hodgkin Lymphoma

A safety management study evaluated whether a prophylactic regimen of tocilizumab and levetiracetam would reduce rates of cytokine release syndrome and neurologic events among patients treated with axicabtagene ciloleucel (Abstract 1547). The regimen was given to 34 patients and consisted of tocilizumab at 8 mg/kg administered on day 2 after the infusion and levetiracetam at 750 mg administered twice on the day of the infusion. Data were compared with those from the ZUMA-1 primary analysis. Grade 3 or higher cytokine release syndrome occurred in 3% of patients who received prophylaxis (1 of 34) vs 13% of patients in the ZUMA-1 trial (13 of 101). Prophylaxis did not reduce the incidence of grade 3 or higher neurologic events (41% in the prophylaxis group vs 28% in ZUMA-1). Blood CAR levels were similar to those observed in ZUMA-1. There were increased levels of serum interleukin (IL) 6, and a trend toward increased levels of interferon (IFN) gamma and granzyme B compared with ZUMA-1. The authors concluded that these findings indicate that the IL-6/IL-6R axis is a major mediator of cytokine release syndrome and multiple cytokines (eg, IL-6, IL-8, IL-15, IFN-gamma, tumor necrosis factor alpha), and may play a role in neurologic events.

lymphoma or transformed follicular lymphoma.

The 108 patients in phases 1 and 2 had a median age of 58 years (range, 23-76 years). One-fourth of patients were ages 65 years or older, and 68%

were male. Stage III/IV disease was present in 83% of patients, 70% had received 3 or more prior therapies, and 23% had developed relapsed disease after undergoing autologous stem cell transplant.

A long-term follow-up analysis of the ZUMA-1 trial was presented by Dr Sattva Neelapu.^{5,6} After a median follow-up of 15.4 months, the investigator-assessed ORR was 82%, including a CR rate of 58%. Responses were ongoing in 42% of patients, with a CR rate of 40%. Durable responses lasting longer than 1 year were observed across all subgroups, including age, refractory status, disease stage, and the International Prognostic Index (IPI) score. The median duration of response for the entire study population was 11.1 months (95% CI, 3.9 months to not reached) and was not reached for patients who achieved a CR (Figure 1). Three patients from the phase 1 portion of the study had an ongoing CR at 24 months. Among 26 patients who achieved a PR, the median duration of response was 1.9 months (95% CI, 1.4-2.1 months). The median progression-free survival (PFS) was 5.8 months (95% CI, 3.3 months to not reached; Figure 2). Median OS was not reached, and the estimated 18-month OS was 52%.

Adverse events (AEs) of grade 3 or higher were observed in 97% of patients, with serious AEs of at least grade 3 observed in 46%. Cytokine release syndrome of grade 3 or higher was observed in 12% of patients, and grade 3 or higher neurologic events occurred in 31%. Among the 4 patients who died (4%), 2 of the deaths were related to treatment. Ten patients experienced a serious AE that occurred later than 6 months after the axicabtagene ciloleucel infusion, with time of onset ranging from 6.7 months to 18.6 months after CAR T-cell therapy. Most of these AEs were infections, such as pneumonia and other lung infections. CAR T cells were detected in 32 of 45 patients (71%) who remained in response at 1 year after therapy. Durable responses were observed in patients with and without persistent, detectable CAR T cells. Biomarker analysis showed that 7 of 21 patients (33%) with progressive disease lacked

CD19 expression in their tumor, and 12 patients (62%) had tumors that expressed programmed death ligand 1 (PD-L1). No cases of replication-competent retrovirus or insertional mutagenesis were observed.

References

1. Crump M. Management of relapsed diffuse B-cell lymphoma. *Hematol Oncol Clin North Am.*

2016;30(6):1195-1213.

2. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood.* 2017;130(16):1800-1808.

3. Yescarta [package insert]. Santa Monica, CA: Kite Pharma, Inc; 2017.

4. Brudno JN, Kochenderfer JN. Chimeric antigen receptor T-cell therapies for lymphoma. *Nat Rev Clin Oncol.* 2018;15(1):31-46.

5. Locke FL, Neelapu SS, Bartlett NL, et al. Primary results from ZUMA-1: a pivotal trial of axicabtagene ciloleucel (axicel; KTE-C19) in patients with refractory

aggressive non-Hodgkin lymphoma (NHL) [AACR abstract CT019]. Presented at: Annual Meeting of the American Association for Cancer Research; April 1-5, 2017; Washington, DC.

6. Neelapu SS, Locke FL, Bartlett NL, et al. Long-term follow-up ZUMA-1: a pivotal trial of axicabtagene ciloleucel (axi-cel; KTE-C19) in patients with refractory aggressive non-Hodgkin lymphoma (NHL) [ASH abstract 578]. *Blood.* 2017;130(suppl 1).

7. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med.* 2017;377(26):2531-2544.

Primary Analysis of JULIET: A Global, Pivotal, Phase 2 Trial of CTL019 in Adult Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma

For patients with relapsed or refractory DLBCL, the standard of care is high-dose chemotherapy followed by autologous stem cell transplant. However, most patients are not eligible for transplant, owing to comorbidities and other factors. Tisagenlecleucel (CTL019) is a CAR T-cell therapy consisting of a CD19 antigen-binding domain, a 4-1BB costimulatory domain, and a CD3-zeta signaling domain.¹⁻³ In a single-center, phase 2 study of 28 patients with relapsed or refractory, CD19-positive lymphoma, tisagenlecleucel yielded an ORR of 64%, including a CR rate of 57%.⁴ After a median follow-up of 29 months, all of the CRs were ongoing. In the DLBCL cohort of 14 patients, the ORR was 50%, with a CR rate of 43%.

JULIET (Study of Efficacy and Safety of CTL019 in Adult DLBCL Patients) was a single-arm, multicenter trial of tisagenlecleucel in patients with relapsed or refractory DLBCL.⁵ Eligible patients had received at least 2 prior lines of therapy, and they had either developed progressive disease after autologous stem cell transplant or were ineligible for the procedure. No prior anti-CD19 therapy was allowed. The primary endpoint was ORR, and

Lugano criteria were used for response assessment by independent review.⁶ The null hypothesis stipulated an ORR of 20% or less. Patients were enrolled at 27 sites in 10 countries across North America, Europe, Australia, and Japan. However, all tisagenlecleucel manu-

facturing occurred at 2 sites: 1 in the United States and 1 in Europe. Among the 147 enrolled patients, 43 withdrew prior to infusion. In 9 of these patients, it was not possible to manufacture the CAR T cells.

Among 99 patients who received

ABSTRACT SUMMARY Risk-Adapted Therapy in Adults With Burkitt Lymphoma: Results of NCI 9177, a Multicenter Prospective Phase II Study of DA-EPOCH-R

A phase 2 trial evaluated risk-adapted therapy in patients with Burkitt lymphoma (Abstract 188). Patients with HIV were eligible for enrollment. Low-risk patients were those with normal lactate dehydrogenase levels, an ECOG performance status of 0 or 1, and no tumor lesion larger than 7 cm. All other patients were considered high risk. Patients received 2 cycles of dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine and prednisone (DA-EPOCH-R), followed by PET imaging. Low-risk patients with a negative imaging scan after the first 2 cycles of treatment received 1 additional cycle of treatment. High-risk patients with a response to the first 2 cycles of DA-EPOCH-R received 4 additional cycles of treatment. Further treatment was guided by imaging results and response to treatment. Among 113 patients, the most common AEs of grade 3 or higher were febrile neutropenia (26%), thrombocytopenia (18.7%), and gastrointestinal/hepatic events (7.7%). After a median follow-up of 35.7 months, the event-free survival was 85.7% (95% CI, 77.3%-91.1%). Event-free survival was 100% for the 14 low-risk patients and 83.4% for the 99 high-risk patients (95% CI, 74.0%-89.7%). Event-free survival was similar for HIV-positive and HIV-negative patients. The treatment was effective for all age groups.

a CAR T-cell infusion, 81 were evaluable for response and had experienced disease progression or had at least 3 months of follow-up. The 99 patients had a median age of 56 years (range, 22-76 years), and 23% were ages 65 years or older. Eighty percent of patients had DLBCL, and the remainder had transformed follicular lymphoma. Fifty-two percent of patients had germinal center B-cell-type disease, and 50% of patients had received 3 or more prior lines of therapy. Forty-seven percent of patients had developed progressive disease after prior autologous stem cell transplant.

The trial met its primary endpoint, with an ORR of 53% (95% CI, 42%-64%; $P < .0001$), including a CR rate of 40%. The response rate was 38% at 3 months, consistent with the long-term benefit observed with this type of therapy. Preplanned subgroup analysis showed a consistent benefit based on age, sex, prior therapy, cell of origin, and disease-related genetic rearrangements. The median duration of response and OS were not reached (Figure 3). Seventy-four percent of patients with a response were relapse-free at 6 months. In nearly all of the patients with a CR at month 3, this response persisted.

In the safety population of 99 patients, any-grade AEs of interest included cytokine release syndrome (58%), prolonged cytopenia (36%), neurologic events (21%), infections (34%), and febrile neutropenia (13%). The most common grade 3/4 AEs of special interest included prolonged cytopenia (27%), cytokine release syndrome (23%), and infection (20%). The median time to onset of cytokine release syndrome was 3 days (range, 1-9 days), with a median duration of 7 days (range, 2-30 days). Eight percent of patients required mechanical

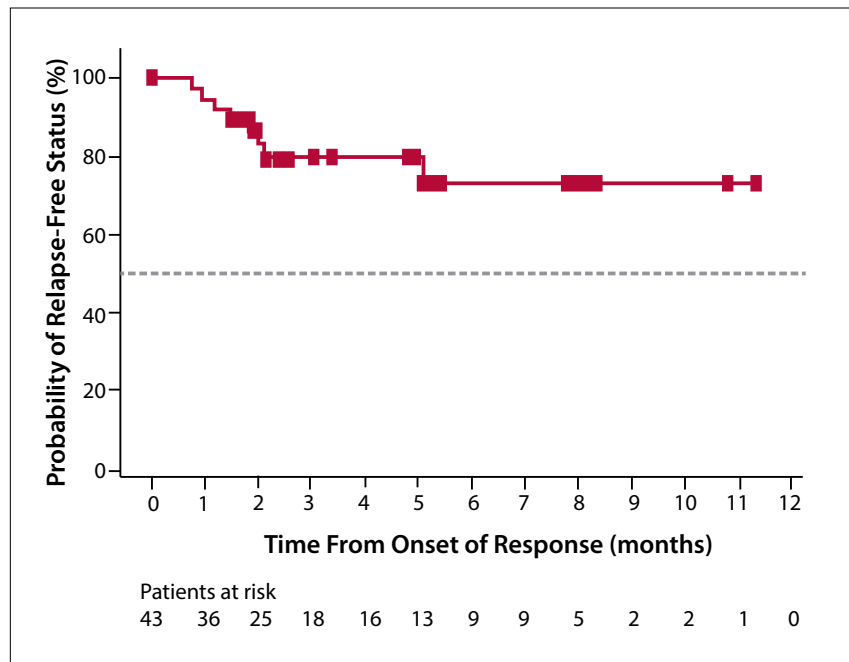


Figure 3. Duration of response in the JULIET trial, which evaluated CTL019 in patients with relapsed or refractory diffuse large B-cell lymphoma. Adapted from Schuster SJ et al. ASH abstract 577. *Blood*. 2017;130(suppl 1).⁵

ventilation. No deaths were caused by CAR T-cell therapy, cytokine release syndrome, or cerebral edema. Quantitative polymerase chain reaction analysis showed that durable responses were associated with persistent transgene levels in the blood. Patients received doses of CAR T cells ranging from 0.6×10^8 to 6×10^8 . However, no relationship was discerned between dose and tumor response, safety, or T-cell expansion after infusion.

References

1. Kalos M, Levine BL, Porter DL, et al. T cells with chimeric antigen receptors have potent antitumor effects and can establish memory in patients with advanced leukemia. *Sci Transl Med*. 2011;3(95):95ra73.
2. Milone MC, Fish JD, Carpenito C, et al. Chimeric receptors containing CD137 signal transduction domains mediate enhanced survival of T cells and increased antileukemic efficacy in vivo. *Mol Ther*. 2009;17(8):1453-1464.

3. Zhang H, Snyder KM, Suhoski MM, et al. 4-1BB is superior to CD28 costimulation for generating CD8+ cytotoxic lymphocytes for adoptive immunotherapy. *J Immunol*. 2007;179(7):4910-4918.
4. Schuster SJ, Svoboda J, Chong EA, et al. Chimeric antigen receptor T cells in refractory B-cell lymphomas. *N Engl J Med*. 2017;377(26):2545-2554.
5. Schuster SJ, Bishop MR, Tam CS, et al. Primary analysis of JULIET: a global, pivotal, phase 2 trial of CTL019 in adult patients with relapsed or refractory diffuse large B-cell lymphoma [ASH abstract 577]. *Blood*. 2017;130(suppl 1).
6. Cheson BD, Fisher RI, Barrington SE, et al; Alliance, Australasian Leukaemia and Lymphoma Group; Eastern Cooperative Oncology Group; European Mantle Cell Lymphoma Consortium; Italian Lymphoma Foundation; European Organisation for Research; Treatment of Cancer/Dutch Hemato-Oncology Group; Grupo Español de Médula Ósea; German High-Grade Lymphoma Study Group; German Hodgkin's Study Group; Japanese Lymphoma Study Group; Lymphoma Study Association; NCIC Clinical Trials Group; Nordic Lymphoma Study Group; Southwest Oncology Group; United Kingdom National Cancer Research Institute. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32(27):3059-3068.

A Comparison of One Year Outcomes in ZUMA-1 (Axicabtagene Ciloleucel) and SCHOLAR-1 in Patients With Refractory, Aggressive Non-Hodgkin Lymphoma

When the ZUMA-1 trial was initiated, outcomes from earlier studies in patients with refractory large B-cell lymphoma had not been fully analyzed in aggregate.¹ The SCHOLAR-1 study (Retrospective Non-Hodgkin Lymphoma Research) was a retrospective, international, multi-institutional, patient-level evaluation of outcomes in 636 patients with refractory NHL.² The study pooled data from 2 observational cohorts and 2 phase 3 clinical trials: CORAL (Collaborative Trial in Relapsed Aggressive Lymphoma) and the National Cancer Institute of Canada Clinical Trials Group LY.12 trial.³⁻⁶ SCHOLAR-1 included patients with DLBCL, primary mediastinal B-cell lymphoma, and transformed follicular lymphoma who had achieved stable or progressive disease as a best response to chemotherapy or had relapsed within 12 months of autologous stem cell transplant. Most patients included in the analysis had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and stage III/IV disease. IPI risk classification was high/intermediate or high in approximately one-fourth of patients.

The overall analysis demonstrated an ORR of 26%, with a CR rate of 7%. Response rates were low across all subgroups, with the lowest rates occurring in patients with a high IPI risk score and those with primary refractory disease. Across refractory subgroups, ORRs ranged from 20% to 39%. Median OS was 6.3 months (95% CI, 5.9-7.0 months). Rates of 1-year and 2-year survival were 28% and 20%, respectively.

A comparative analysis was conducted to evaluate outcomes from ZUMA-1 and SCHOLAR-1.⁷ Several methods were used to compensate for

performing a cross-study comparison between a prospective clinical trial and a retrospective analysis. Propensity score methods were used to balance patient prognostic factors between the 2 studies. Covariates that were used in the comparative analysis were chosen by a statistician who was blinded to the outcomes. Propensity scores were derived to create a common support data set for the 2 studies, and these propensity scores were used to estimate average treatment differences between the 2 studies. The 2 studies used a common definition of “refractory.”

The comparative analysis included 101 patients from ZUMA-1 and 508 from SCHOLAR-1. In the ZUMA-1 cohort, 67% were male, 24% were ages 65 years or older, and all of the patients had an ECOG performance status of 0 or 1. In the SCHOLAR-1 cohort, 64% were male, 15% were ages 65 years or older, and 20% had an ECOG performance status of 2 to 4. In the ZUMA-1 cohort, more patients had stage III/IV disease (85% vs 67%), an IPI score of 3 or higher (48% vs 35%), and a history of at least 3 prior lines of therapy (69% vs 26%). More

patients in the SCHOLAR-1 cohort had undergone stem cell transplant for refractory disease (32% vs 14%).

The median follow-up was 15.1 months for the ZUMA-1 cohort and ranged from 7.6 years to 14.8 years for the SCHOLAR-1 cohort. The study adjusted for age, sex, prior therapy, refractory subgroup, stem cell transplant status, and ECOG performance status. After this adjustment, 101 patients were evaluable from the ZUMA-1 trial. In SCHOLAR-1, 422 patients were evaluable for response and 412 were evaluable for survival. In the population of 535 evaluable patients for the propensity analysis, 64% were male, 15% were ages 65 years or older, and 100% had an ECOG performance status of 0 or 1. Seventy-two percent of patients had stage III/IV disease, 35% had an IPI score of 3 or higher, 31% had received 3 or more prior lines of therapy, and 30% had undergone stem cell transplant at any time after the diagnosis of refractory disease.

Propensity score analysis yielded an ORR of 83% for CAR T-cell therapy vs 33% for all other therapies (Table 1), reflecting a treatment dif-

Table 1. One-Year Outcomes in ZUMA-1 vs SCHOLAR-1

	ZUMA-1 Updated Analysis ¹	Propensity Score Analysis ² (N=523)	
	(N=108)	CAR T-Cell Therapy	Non-CAR T-Cell Therapy
ORR, %	82	83	33
Treatment difference, %	–	49 (95% CI, 33-63)	
CR, %	58	57	12
Treatment difference, %	–	46 (95% CI, 26-59)	

CAR, chimeric antigen receptor; CR, complete response; ORR, overall response rate.

Adapted from Neelapu SS et al. ASH abstract 579. *Blood*. 2017;130(suppl 1).⁷

ference of 49% (95% CI, 33%-63%). The CR rate was 57% for CAR T-cell therapy vs 12% for non-CAR T-cell therapy, reflecting a treatment difference of 46% (95% CI, 26%-59%). Similar results were obtained from an additional analysis that included 8 covariates, accounting for IPI score and disease stage. Propensity score analysis yielded a median OS of 16.4 months (95% CI, 11.5 months to not reached) with CAR T-cell therapy vs 5.4 months (5.0-6.4 months) with other therapies (hazard ratio [HR], 0.28; 95% CI, 0.15-0.40). The 12-month OS was 73% with CAR T-cell therapy vs 26% with other therapies, and 18-month OS rates were 47% vs 23%, respectively.

In summary, treatment with CAR T-cell therapy was estimated to provide

an increase in the CR rate of approximately fivefold, and the 12-month OS rate improved by approximately threefold. CAR T-cell therapy conferred a 72% reduction in the risk of death in patients with refractory large B-cell lymphoma compared with other therapies.

References

1. Neelapu SS, Locke FL, Bartlett NL, et al. Long-term follow-up ZUMA-1: a pivotal trial of axicabtagene ciloleucel (axi-cel; KTE-C19) in patients with refractory aggressive non-Hodgkin lymphoma (NHL) [ASH abstract 578]. *Blood*. 2017;130(suppl 1).
2. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood*. 2017;130(16):1800-1808.
3. Crump M, Kuruvilla J, Couban S, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplanta-

tion for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. *J Clin Oncol*. 2014;32(31):3490-3496.

4. Gisselbrecht C, Schmitz N, Mounier N, et al. Rituximab maintenance therapy after autologous stem-cell transplantation in patients with relapsed CD20(+) diffuse large B-cell lymphoma: final analysis of the collaborative trial in relapsed aggressive lymphoma. *J Clin Oncol*. 2012;30(36):4462-4469.

5. Maurer MJ, Ghesquière H, Jais JP, et al. Event-free survival at 24 months is a robust end point for disease-related outcome in diffuse large B-cell lymphoma treated with immunochemotherapy. *J Clin Oncol*. 2014;32(10):1066-1073.

6. Ahmed MA, Chihara D, Vargas N, et al. Outcome of relapsed/refractory diffuse large B-cell lymphoma after second salvage therapy: MD Anderson experience [ICML abstract 375]. *Hematol Oncol*. 2015;33(suppl 1).

7. Neelapu SS, Locke FL, Bartlett NL, et al. A comparison of one year outcomes in ZUMA-1 (axicabtagene ciloleucel) and SCHOLAR-1 in patients with refractory, aggressive non-Hodgkin lymphoma (NHL) [ASH abstract 579]. *Blood*. 2017;130(suppl 1).

High Durable CR Rates in Relapsed/Refractory (R/R) Aggressive B-NHL Treated With the CD19-Directed CAR T Cell Product JCAR017 (TRANSCEND NHL 001): Defined Composition Allows for Dose-Finding and Definition of Pivotal Cohort

Lisocabtagene maraleucel, also known as JCAR017, is a CD19-directed CAR T-cell product consisting of individually formulated CD4-positive and CD8-positive cell suspensions that are administered in a defined composition, using controlled doses of cells. Lisocabtagene maraleucel has a 4-1BB costimulatory domain and signals through CD3-zeta. CD19 binding is provided by a single-chain Fv moiety. A truncated epidermal growth factor domain enables tracking and quantification of the product, but is not capable of intracellular signaling. After apheresis, patient cells are immunomagnetically selected and separated based on CD4 or CD8 expression. The 2 cell types are separately transduced with a lentiviral vector, followed by expansion. The

modified cells are then administered using equal numbers of CD4-positive and CD8-positive cells.

The phase 1 TRANSCEND NHL trial (Study Evaluating the Safety and Pharmacokinetics of JCAR017 in B-Cell Non-Hodgkin Lymphoma) was designed to determine the preferred regimen and study population for testing in a planned pivotal cohort.¹ In the initial dose-finding cohorts, lisocabtagene maraleucel was administered as a single dose of 5×10^7 cells, a double dose of 5×10^7 cells, or a single dose of 1×10^8 cells. The single-dose cohorts were chosen for expansion, and the single dose of 1×10^8 cells was chosen for the pivotal cohort of DLBCL patients. Data were available from 91 patients in the DLBCL cohort (cohort 1) and 67 patients who met the inclusion

criteria for the planned pivotal cohort (cohort 2). All patients had DLBCL that had progressed after 2 prior lines of therapy. Cohort 2 included patients with DLBCL, either de novo DLBCL, transformed follicular lymphoma, or high-grade B-cell lymphoma with 2 or 3 gene rearrangements involving *c-MYC*, *BCL2*, or *BCL6*. Cohort 1 included the same patients, plus those with DLBCL transformed from chronic lymphocytic leukemia or marginal zone lymphoma, primary mediastinal B-cell lymphoma, or stage IIIB follicular lymphoma. The criteria permitted enrollment of patients who had undergone prior stem cell transplant and who had secondary central nervous system involvement. No minimum absolute lymphocyte count was required for apheresis. However,

ABSTRACT SUMMARY ACTR087, Autologous T Lymphocytes Expressing Antibody Coupled T-Cell Receptors (ACTR), Induces Complete Responses in Patients With Relapsed or Refractory CD20-Positive B-Cell Lymphoma, in Combination With Rituximab

Antibody-coupled T-cell receptor (ACTR) therapy combined with rituximab was investigated in the ATTCK-20-2 trial (Study of ACTR087 in Subjects With Relapsed or Refractory B-Cell Lymphoma) of patients with relapsed or refractory CD20-positive B-cell lymphoma (Abstract 580). All patients in the study received cyclophosphamide (500 mg/m²) and fludarabine (30 mg/m²) for 3 days, followed by rituximab (375 mg/m²) and ACTR087 treatment. Patients in cohort 1 received a target dose of 0.5 × 10⁶ ACTR-positive cells/kg, and patients in cohort 2 received a dose of 1.5 × 10⁶ ACTR-positive cells/kg. Seven patients were enrolled into cohort 1 and 10 into cohort 2. Patients were heavily pretreated. Most were refractory to their most recent therapy. Dose-dependent expansion of ACTR T cells was observed, as was sustained persistence in the presence of rituximab. Toxicity was generally manageable at the lower dose level. One patient developed a dose-limiting toxicity of grade 4 thrombocytopenia that lasted for more than 14 days and ultimately resolved. Cytokine release syndrome and neurotoxicity, along with other AEs associated with T-cell activation, were evident at the higher dose level. A response was seen in 5 of 10 evaluable patients. One patient had an ongoing CR.

patients with prior allogeneic stem cell transplant were not included in the pivotal cohort.

Enrolled patients underwent apheresis. Afterward, lisocabtagene maraleucel products were manufactured, and patients were allowed to receive bridging chemotherapy for disease stabilization. Positron emission tomography (PET)-positive disease was confirmed among patients who received treatment with bridging chemotherapy. Patients were then treated with fludarabine (30 mg/m²) and cyclophosphamide (300 mg/m²) for 3 days, followed by lisocabtagene maraleucel 2 to 7 days later.

The overall study population included 45 patients treated with 1 dose of 5 × 10⁷ cells, 6 patients treated with 2 doses of 5 × 10⁷ cells, and 40 patients treated with 1 dose of 1 × 10⁸ cells. The 91 patients in cohort 1 had a median age of 61 years (range, 20-82 years), and 34% were ages 65 years or older. Two-thirds of patients had DLBCL not otherwise specified, and 21% had transformed follicular lymphoma. One-fifth of patients had 2 or 3 gene rearrangements. Forty-two percent had an IPI score of 3 or higher, and 77% had stage III/IV disease. In cohort 2, the median age was 60 years (range, 20-82 years), and 36% were ages 65 years or older. Three-fourths of patients had DLBCL, and 24% had transformed follicular lymphoma. Two or 3 gene rearrangements were present in 24% of patients. Thirty-six percent of patients had an IPI score of at least 3, and 72% of patients had stage III/IV disease. Approximately half of patients in each cohort had never achieved a CR. In both cohorts, patients had received a median of 3 lines of prior therapy.

In the entire study population, the most common treatment-emergent AEs of any grade were neutropenia, thrombocytopenia, and anemia. Neutropenia and thrombocytopenia were also the most common grade 3/4 AEs. Cytokine release syndrome occurred

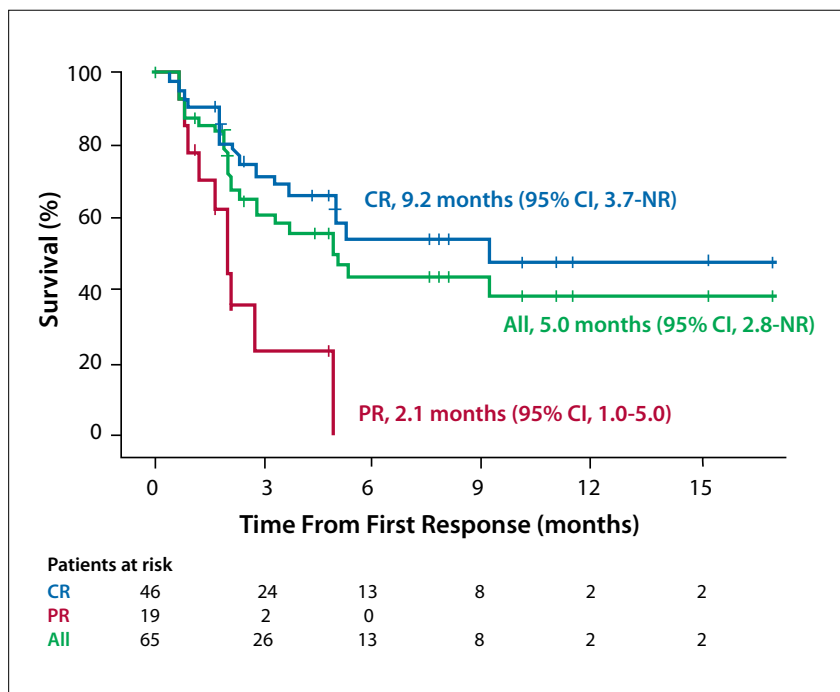


Figure 4. Durability of response in the full cohort of patients with high-risk DLBCL treated with JCAR017 in the phase 1 TRANSCEND NHL trial. CR, complete response; DLBCL, diffuse large B-cell lymphoma; NR, not reached; PR, partial response. Adapted from Abramson JS et al. ASH abstract 581. *Blood*. 2017;130(suppl 1).¹

in 35% of patients; these events were grade 1 or 2 in all but 1 patient, who had a grade 4 event. Neurotoxicity of any grade was observed in 19% of patients; 12% of cases were grade 3/4. No patients died from cytokine release syndrome or neurotoxicity. The median time to onset was 5 days (range, 1-14 days) for cytokine release syndrome and 10 days (range, 3-23 days) for neurotoxicity. Twelve percent of patients were treated with tocilizumab and 16% with dexamethasone. Toxicities in cohort 2 generally mirrored those observed for the entire study population.

In the entire study population, the

ORR was 74% (95% CI, 63%-83%), with a CR rate of 52% (95% CI, 41%-63%). Patients in cohort 2 had an ORR of 80% (95% CI, 68%-89%), with a CR rate of 55% (95% CI, 43%-68%). In cohort 1, among 54 patients with at least 6 months of follow-up, the 6-month ORR was 35% (95% CI, 23%-49%), and the 6-month CR rate was 31% (95% CI, 20%-46%). In cohort 2, among 38 patients with at least 6 months of follow-up, 6-month ORR was 47% (95% CI, 31%-64%), and the 6-month CR rate was 42% (95% CI, 26%-59%). In cohort 1, the median duration of response was 5.0 months (95% CI, 2.8 months

to not reached). In cohort 2, the median duration of response was 9.2 months (95% CI, 3.7 months to not reached; Figure 4). Durable responses were observed across most subgroups. Median OS was not reached (95% CI, 9.0 months to not reached) in cohort 1 or cohort 2 (95% CI, not reached to not reached).

Reference

1. Abramson JS, Palomba ML, Gordon LI, et al. High durable CR rates in relapsed/refractory (R/R) aggressive B-NHL treated with the CD19-directed CAR T cell product JCAR017 (TRANSCEND NHL 001): defined composition allows for dose-finding and definition of pivotal cohort [ASH abstract 581]. *Blood*. 2017;130(suppl 1).

Phase 1 Results From ZUMA-6: Axicabtagene Ciloleucel (axi-cel; KTE-C19) in Combination With Atezolizumab for the Treatment of Patients With Refractory Diffuse Large B-Cell Lymphoma

In the phase 1/2 ZUMA-6 trial (A Study Evaluating KTE-C19 in Combination With Atezolizumab in Subjects With Refractory Diffuse Large B-Cell Lymphoma [DLBCL]), patients with refractory DLBCL received treatment with axicabtagene ciloleucel plus atezolizumab, a humanized antibody that binds to PD-L1.¹ Eligible patients had received at least 1 prior line of therapy that included a CD20-targeting agent and an anthracycline. Patients had developed stable or progressive disease after their most recent line of therapy or had relapsed following autologous stem cell transplant. Enrolled patients received low-dose conditioning with fludarabine (30 mg/m² daily) plus cyclophosphamide (500 mg/m² daily) for 3 days, followed by axicabtagene ciloleucel infusion using a target dose of 2×10^6 cells/kg. Four doses of atezolizumab (1200 mg, every

3 weeks) were administered starting on day 21 after axicabtagene ciloleucel infusion in cohort 1, on day 14 in cohort 2, and on day 1 in cohort 3. The primary endpoint was dose-limiting toxicities occurring within 21 days of the antibody dose.

Out of 10 patients enrolled, 1 withdrew owing to an AE prior to receiving treatment. Three patients in cohort 1 and 3 patients in cohort 2 had completed treatment with all 4 doses of atezolizumab. Two patients in cohort 3 had received 3 doses of atezolizumab. One patient in cohort 3 received only 1 dose of atezolizumab, missing the others owing to toxicity. Median follow-up was 5.8 months. Two-thirds of patients had stage III/IV disease, and 22% of patients had an IPI score of 3 or 4. Two patients (22%) had B symptoms, and 3 (33%) had bulky disease.

The ORR was 89% and included a

CR rate of 56%. Three patients (33%) developed disease progression following a response. Eighty-eight percent of atezolizumab doses were delivered. Two patients (22%) experienced a PR to CR conversion at 6 and 9 months after axicabtagene ciloleucel infusion.

The administration of atezolizumab after infusion with axicabtagene ciloleucel did not increase the use of tocilizumab or corticosteroids. No grade 5 AEs were reported. All patients experienced an AE of any grade, and all experienced an AE of any grade that was related to axicabtagene ciloleucel treatment. Only 44% of patients experienced an AE of any grade related to atezolizumab treatment. Eight patients (89%) experienced a grade 3/4 AE. The most common treatment-emergent grade 3/4 AEs were anemia (78%), encephalopathy (56%), and neutropenia (44%). One patient in cohort 3 experienced a dose-limiting

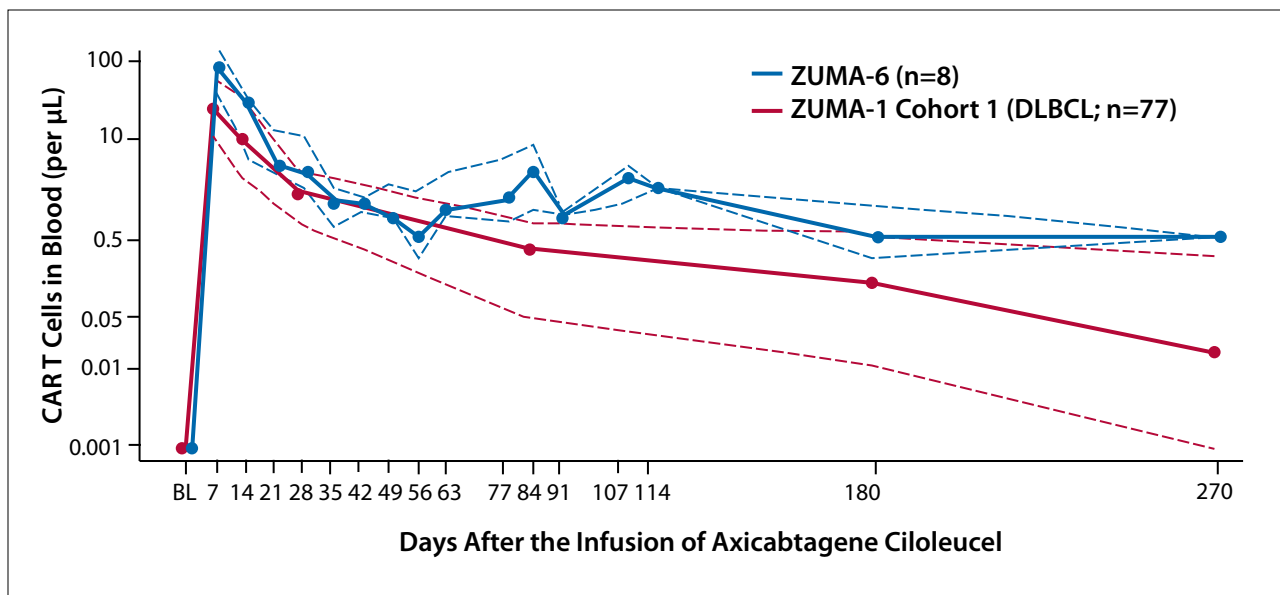


Figure 5. Postinfusion kinetics of CAR T cells in the blood of patients from the ZUMA-6 and ZUMA-1 trials. ZUMA-6 is evaluating axicabtagene ciloleucel in combination with atezolizumab in patients with refractory DLBCL. The dashed lines show the interquartile (Q1-Q3) range. BL, baseline; CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma. Adapted from Locke FL et al. ASH abstract 2826. *Blood.* 2017;130(suppl 1).¹

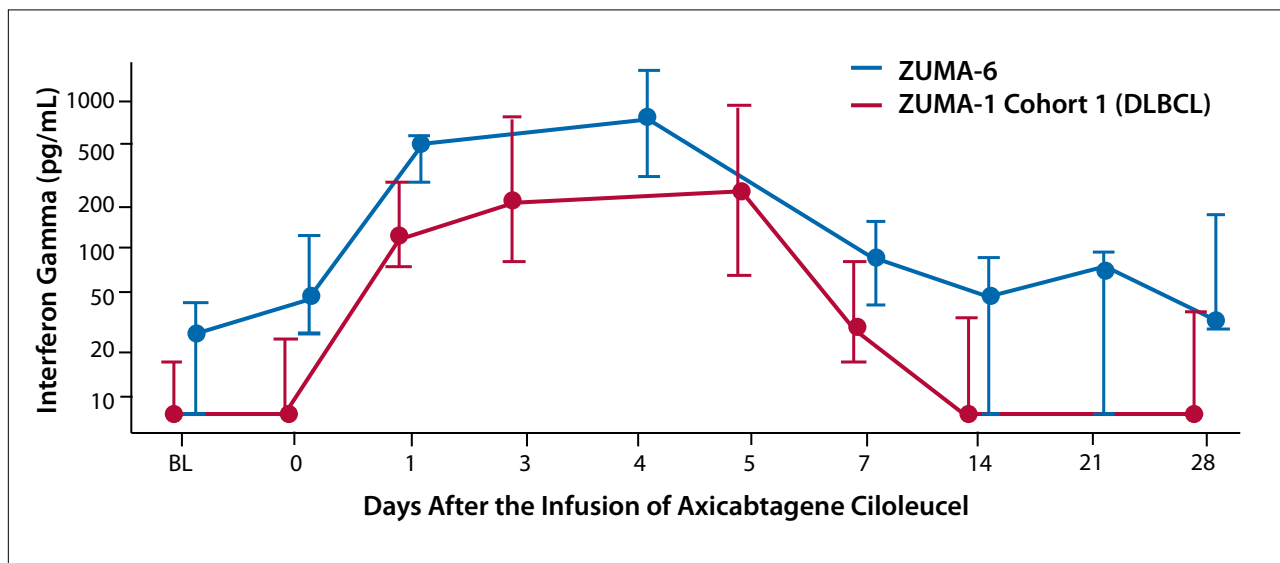


Figure 6. The addition of atezolizumab to axicabtagene ciloleucel CAR T-cell treatment was not associated with meaningful changes in cytokine levels. Levels of interferon gamma are shown here. DLBCL, diffuse large B-cell lymphoma. Adapted from Locke FL et al. ASH abstract 2826. *Blood.* 2017;130(suppl 1).¹

toxicity consisting of grade 3 anemia, grade 4 thrombocytopenia, and grade 4 neutropenia, all of which were considered related to study treatment.

The postinfusion kinetics of CAR T cells in the blood are shown in Figure 5. The addition of atezolizumab

to axicabtagene ciloleucel CAR T-cell treatment was not associated with meaningful changes in cytokine levels (Figure 6).

The study is ongoing. At the time of the analysis, additional patients were being enrolled into cohort 3.

Reference

1. Locke FL, Westin JR, Miklos DB, et al. Phase 1 results from ZUMA-6: axicabtagene ciloleucel (axi-cel; KTE-c19) in combination with atezolizumab for the treatment of patients with refractory diffuse large B cell lymphoma (DLBCL) [ASH abstract 2826]. *Blood.* 2017;130(suppl 1).

Effect of Rituximab in Primary Central Nervous System Lymphoma—Results of the Randomized Phase III HOVON 105/ALLG NHL 24 Study

A phase 3 study from the Hematology Oncology Foundation for Adults in the Netherlands/Australian Leukemia and Lymphoma Group investigated the efficacy of rituximab in the treatment of primary central nervous system lymphoma (PCNSL).¹ Use of rituximab in this setting is based primarily on extrapolation of data from patients with B-cell lymphoma and retrospective studies of PCNSL patients. However, rituximab is a large molecule that could have low rates of penetration through the blood-brain barrier, reducing its efficacy. Eligible patients were ages 18 to 70 years with newly diagnosed PCNSL and an ECOG performance status of 0 to 3.

After stratification for age and performance status, patients were randomly assigned to receive treatment with 2 cycles of high-dose methotrexate (3000 mg/m² on days 1 and 15), carmustine (100 mg/m² on day 4), teniposide (100 mg/m² on days 2 and

3), and methylprednisolone (60 mg/m² on days 1-5; MBVP), with or without rituximab. Rituximab (375 mg/m²) was administered weekly during cycle 1 and every other week during cycle 2 for a total of 6 cycles. Patients whose cerebrospinal fluid was positive after the first treatment cycle received intrathecal methotrexate. Patients who achieved a PR or CR received consolidation treatment with high-dose cytarabine (2000 mg/m² every 12 hours on days 1 to 2). Patients ages 60 years or younger received 30 Gy of whole brain radiotherapy, with an additional 10 Gy for patients with a PR. Patients ages 61 years or older did not receive radiotherapy treatment. Evaluation with magnetic resonance imaging was planned after 2 treatment cycles, after high-dose cytarabine, and again 4 weeks after whole brain radiotherapy. The primary endpoint was 1-year event-free survival. The trial design assumed a 1-year event-free survival

of 75% in the rituximab-MBVP arm vs 60% in the MBVP-alone arm, corresponding to an HR of 0.56.

The study randomly assigned 100 patients to the MBVP-alone arm and 99 to the rituximab-MBVP arm. Patients had a median age of 61 years (range, 26-70 years). The control arm had a higher proportion of men (61% vs 48%). Other patient characteristics were well-balanced between the 2 arms. Twenty-nine percent of patients had elevated lactate dehydrogenase, and 30% had positive cerebrospinal fluid. All patients received cycle 1 treatment, 90% received cycle 2 treatment, and 81% received high-dose cytarabine. Eight patients in each arm received intrathecal methotrexate. Whole brain radiotherapy was administered to 34% of patients in the control arm and 36% in the rituximab-MBVP arm.

After induction, the ORR was 86% in each arm, with CR rates of 36% in the MBVP-alone arm and 30% in the rituximab-MBVP arm. In patients ages 60 years or younger, the ORR was 92% in both arms, with CR rates of 30% to 32%. In patients older than 60 years, the ORR was 83% in the MBVP-alone arm, with a 42% CR rate, vs 80% in the rituximab-MBVP arm, with a 29% CR rate. At the end of treatment, the CR rate was 66% with MBVP vs 68% with the addition of rituximab. In patients ages 60 years or younger, the CR rate was 72% in the MBVP arm vs 85% in the rituximab-MBVP arm. In patients older than 60 years, the CR rates were 60% vs 52%, respectively.

One-year event-free survival was 49% in the MBVP arm and 52% with the addition of rituximab (HR, 1.00; 95% CI, 0.70-1.43; *P*=.99; Figure 7). Median event-free survival was 10.8 months in the MBVP-alone arm vs

ABSTRACT SUMMARY R-GCVP as Second Line Treatment in Elderly Patients With DLBCL Who Fail R-CHOP and Are Not Candidates for Intensive Therapy

A retrospective study investigated the combination of rituximab, gemcitabine, cyclophosphamide, vincristine, and prednisolone (R-GCVP) as second-line treatment of patients with relapsed or refractory DLBCL who were not candidates for intensive treatment (Abstract 4133). The study enrolled 24 adults who were considered unfit for high-dose therapy by their primary treating physician and who received R-GCVP as their second or later line of treatment. The patients had a median age of 77 years (range, 40-85 years) and a median ECOG performance status of 2 (range, 0-3). Most patients (n=15) had at least 1 comorbidity. Three-fourths of patients had de novo DLBCL. Patients had received a median of 1 line of prior therapy (range, 1-3). Patients completed a median of 4 cycles (range, 1-6) of R-GCVP, and 72% of patients completed the planned therapy. Infection was the most common nonhematologic toxicity, occurring in two-thirds of patients. No deaths were attributed to treatment toxicity. The ORR was 83% and included a CR rate of 42%. Median OS was 11 months, and median PFS was 8 months.

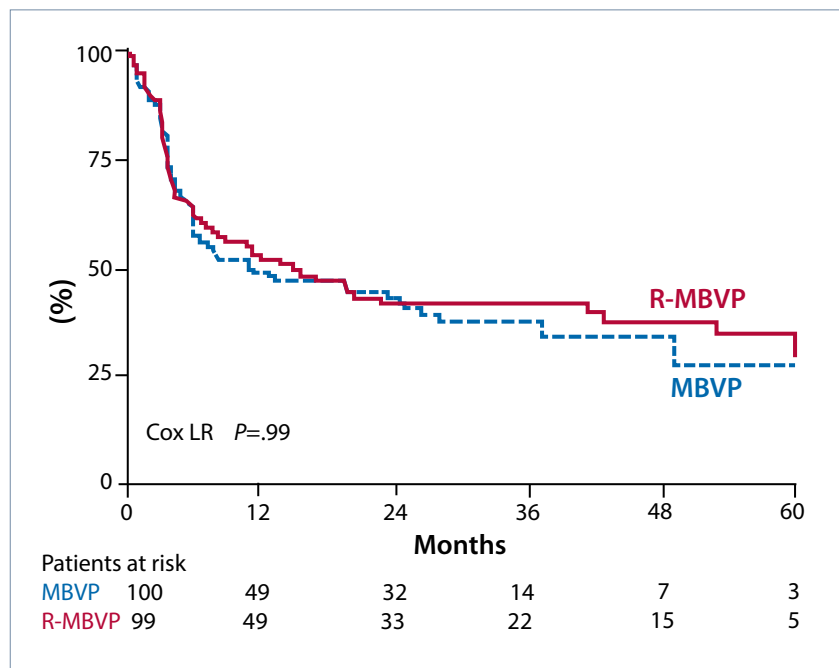


Figure 7. Event-free survival in a trial evaluating the addition of rituximab to MBVP. LR, likelihood ratio; MBVP, methotrexate, carmustine, teniposide, and methylprednisolone; R, rituximab. Adapted from Bromberg J et al. ASH abstract 582. *Blood*. 2017;130(suppl 1).¹

14.9 months in the rituximab-MBVP arm. An exploratory analysis suggested a possible benefit in patients 60 years or younger (HR, 0.56; $P=.054$). No benefit was observed for older patients

(HR, 1.42; $P=.129$). Median PFS was similar for both arms (HR, 0.77; 95% CI, 0.52-1.13; $P=.18$). Among the 120 patients who were still alive at the time of the analysis, the median follow-up

was 32.9 months (range, 3.6-79.2 months). However, no difference in OS was observed for the 2 arms (HR, 0.93; 95% CI, 0.59-1.44; $P=.74$).

Grade 3/4 AEs were observed after induction in 56% of patients in the control arm and 59% of patients in the rituximab-MBVP arm. After treatment with high-dose cytarabine, grade 3/4 AEs were observed in 22% of patients in the MBVP-alone arm and 14% of patients in the rituximab-MBVP arm. In the MBVP arm, 41 patients died, including 29 (71%) from PCNSL, 3 (7%) from a treatment-related complication, 2 (5%) from intercurrent disease, and 7 (17%) from other causes. In the rituximab-MBVP arm, 38 patients died, 29 (76%) from PCNSL, 2 (5%) from intercurrent disease, 1 (3%) from treatment-related complications, 1 (3%) from secondary malignancy, and 5 (13%) from other causes.

Reference

1. Bromberg J, Issa S, Bukanina K, et al. Effect of rituximab in primary central nervous system lymphoma—results of the randomized phase III HOVON 105/ALLG NHL 24 study [ASH abstract 582]. *Blood*. 2017;130(suppl 1).

Encouraging Early Results From the First in-Human Clinical Trial of ADCT-402 (Loncastuximab Tesirine), a Novel Pyrrolobenzodiazepine-Based Antibody Drug Conjugate, in Relapsed/Refractory B-Cell Lineage Non-Hodgkin Lymphoma

Loncastuximab tesirine (ADCT-402) is an antibody-drug conjugate consisting of an anti-CD19 antibody conjugated to a pyrrolobenzodiazepine dimer that induces DNA crosslinks.¹ Upon binding to CD19, the antibody-drug conjugate is internalized, after which protease activity cleaves the linker, and the DNA crosslinking agent is released. The pyrrolobenzodiazepine dimer binds in the minor groove of the DNA double

helix, providing some protection from DNA repair mechanisms.² The DNA crosslinking agent has picomolar potency and has demonstrated potent antitumor activity against multidrug-resistant cell lines, in preclinical cancer models, and in slowly proliferating cancers.³⁻⁵

A multicenter, open-label, phase 1, dose-escalation and expansion study evaluated loncastuximab tesirine in patients with relapsed or refractory

NHL.⁶ During the dose-escalation portion of the first-in-human study, patients received a 1-hour intravenous infusion of loncastuximab tesirine at doses ranging from 15 $\mu\text{g}/\text{kg}$ to 200 $\mu\text{g}/\text{kg}$. Dose escalation followed a 3 + 3 methodology. Patients had relapsed B-cell NHL, measurable disease as defined by the Lugano classification, and an ECOG performance status of 0 to 2, with adequate neutrophil, platelet, and hemoglobin levels.⁷ The

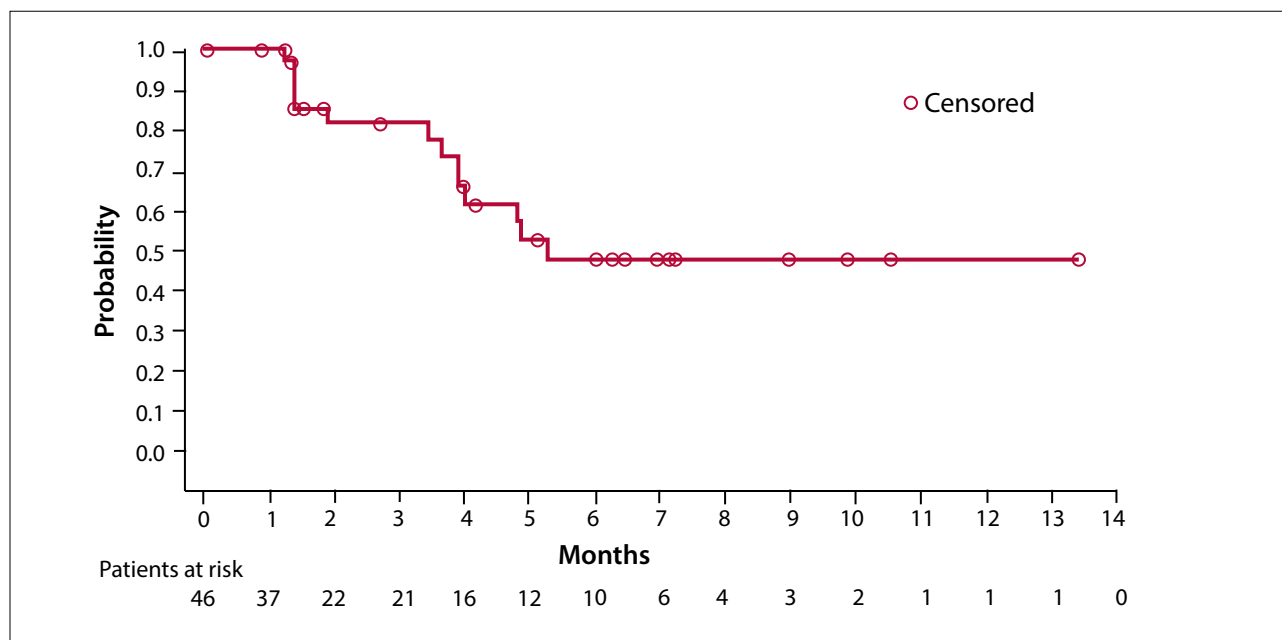


Figure 8. Duration of response from the first in-human clinical trial of loncastuximab tesirine (ADCT-402) in relapsed/refractory B-cell non-Hodgkin lymphoma. Adapted from Kahl BS et al. ASH abstract 187. *Blood*. 2017;130(suppl 1).⁶

study included 138 patients, with a median age of 63.5 years (range, 23-86 years). Most patients (68.8%) were male, and 58% had refractory disease. Patients had received a median of 3 (range, 1-10) prior lines of therapy, and 25.4% had received prior stem cell transplant. The most common diagnosis was DLBCL (68.8%), followed by follicular lymphoma (8.7%), mantle cell lymphoma (8.7%), and marginal zone B-cell lymphoma (3.6%).

Across the entire study population, patients received a median of 2 (range, 1-22) cycles of loncastuximab tesirine. A treatment-emergent AE of any grade occurred in 135 patients (97.8%). The most common treatment-emergent AEs of any grade were skin-related changes (52.2%), fatigue (44.2%), and nausea (28.3%). Treatment-emergent AEs of grade 3 or higher were reported in 63.8% of patients, and those observed in at least 10% of patients included neutropenia (15.2%), increased gamma-glutamyl-transferase (14.5%), anemia (12.3%), and thrombocytopenia (12.3%). Sixteen patients (11.6%) withdrew from the study owing to toxicity. One dose-

limiting toxicity of thrombocytopenia was observed in a patient who received the highest dose (200 $\mu\text{g}/\text{kg}$) of loncastuximab tesirine. The maximum tolerated dose was not reached. Excessive toxicities appeared after the second and third treatment cycles in patients who received the highest dose of loncastuximab tesirine. In light of these toxicities, the doses of 120 $\mu\text{g}/\text{kg}$ and 150 $\mu\text{g}/\text{kg}$ were chosen for expansion.

Among 85 patients available for response evaluation, the ORR was 54.2%, with a CR rate of 31.8%. In 68 patients who received the study compound at a dose of 120 $\mu\text{g}/\text{kg}$ or higher, the ORR was 60.3%, with a CR rate of 35.3%. The median duration of response was 5.3 months, and the median PFS was 4.8 months (Figure 8). Among the 59 evaluable patients with DLBCL, the ORR was 49.1%, with a CR rate of 32.2%. For DLBCL patients who received loncastuximab tesirine doses of 120 $\mu\text{g}/\text{kg}$ or higher, the ORR was 55.1%, with a CR rate of 36.7%. DLBCL patients had a median duration of response of 4.9 months, and a median PFS of approximately 3.5 months. Pharmacokinetic analysis

showed higher peak concentrations of study drug in patients who received higher doses. Enrollment is continuing into expansion cohorts at doses of 120 $\mu\text{g}/\text{kg}$ and 150 $\mu\text{g}/\text{kg}$.

References

- Hartley JA. The development of pyrrolobenzodiazepines as antitumor agents. *Expert Opin Investig Drugs*. 2011;20(6):733-744.
- Clingen PH, De Silva IU, McHugh PJ, et al. The XPF-ERCC1 endonuclease and homologous recombination contribute to the repair of minor groove DNA interstrand crosslinks in mammalian cells produced by the pyrrolo[2,1-c][1,4]benzodiazepine dimer SJG-136. *Nucleic Acids Res*. 2005;33(10):3283-3291.
- Tiberghien AC, Levy JN, Masterson LA, et al. Design and synthesis of tesirine, a clinical antibody-drug conjugate pyrrolobenzodiazepine dimer payload. *ACS Med Chem Lett*. 2016;7(11):983-987.
- Kung Sutherland MS, Walter RB, Jeffrey SC, et al. SGN-CD33A: a novel CD33-targeting antibody-drug conjugate using a pyrrolobenzodiazepine dimer is active in models of drug-resistant AML. *Blood*. 2013;122(8):1455-1463.
- Hartley JA, Hamaguchi A, Coffils M, et al. SG2285, a novel C2-aryl-substituted pyrrolobenzodiazepine dimer prodrug that cross-links DNA and exerts highly potent antitumor activity. *Cancer Res*. 2010;70(17):6849-6858.
- Kahl BS, Hamadani M, Caimi P, et al. Encouraging early results from the first in-human clinical trial of ADCT-402 (loncastuximab tesirine), a novel pyrrolobenzodiazepine-based antibody drug conjugate, in relapsed/refractory B-cell lineage non-Hodgkin lymphoma [ASH abstract 187]. *Blood*. 2017;130(suppl 1).
- Cheson BD, Fisher RI, Barrington SF, et al; Alliance,

Australasian Leukaemia and Lymphoma Group; Eastern Cooperative Oncology Group; European Mantle Cell Lymphoma Consortium; Italian Lymphoma Foundation; European Organisation for Research; Treatment of Cancer/Dutch Hemato-Oncology Group;

Grupo Español de Médula Ósea; German High-Grade Lymphoma Study Group; German Hodgkin's Study Group; Japanese Lymphoma Study Group; Lymphoma Study Association; NCIC Clinical Trials Group; Nordic Lymphoma Study Group; Southwest Oncology Group;

United Kingdom National Cancer Research Institute. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32(27):3059-3068.

Advances in Aggressive Lymphoma From the 2017 American Society of Hematology Annual Meeting and Exposition: Commentary

Frederick L. Locke, MD

Vice Chair and Associate Member
Department of Blood and Marrow Transplant
and Cellular Immunotherapy
Moffitt Cancer Center
Tampa, Florida

Faysal Haroun, MD

Assistant Professor of Medicine
Division of Hematology and Oncology
George Washington School of Medicine
and Health Sciences
Washington, DC

Several studies in aggressive lymphoma presented at the 2017 American Society of Hematology (ASH) meeting have the potential to impact clinical practice. Data for chimeric antigen receptor (CAR) T-cell therapy continue to support the use of these agents in lymphoma. Studies were presented on axicabtagene ciloleucel, as well as tisagenlecleucel and JCAR017. Other studies focused on rituximab in patients with primary central nervous system lymphoma; the CD19 monoclonal antibody drug conjugate ADCT-402 in patients with relapsed or refractory B-cell non-Hodgkin lymphoma; and rituximab, gemcitabine, cyclophosphamide, vincristine, and prednisolone (R-GCVP) as second-line treatment of elderly patients with diffuse large B-cell lymphoma (DLBCL).

CAR T-Cell Therapy

Axicabtagene Ciloleucel

Dr Sattva Neelapu presented a long-term follow-up analysis of ZUMA-1 (A Phase 1-2 Multi-Center Study Evaluating Axicabtagene Ciloleucel in Subjects With Refractory Aggressive Non-Hodgkin Lymphoma), the pivotal trial of axicabtagene ciloleucel (also known as axi-cel; formerly,

KTE-C19) in patients with refractory, aggressive non-Hodgkin lymphoma.¹ Axicabtagene ciloleucel is a second-generation, anti-CD19, CAR T-cell therapy with a CD28 costimulatory domain. ZUMA-1 was a phase 1/2 trial in patients with refractory DLBCL, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma.² Patients treated in the trial had not responded to their last line of therapy; at best, they had stable disease or had progressed within 12 months of an autologous transplant. Historical data for these types of patients suggest a dismal chance of response with standard chemotherapies, with an objective response rate of 26% and a complete response rate of 7%.³

Dr Locke was co-first author of the long-term analysis of ZUMA-1, which was simultaneously presented at the 2017 ASH meeting and published in the *New England Journal of Medicine*.⁴ The long-term analysis combined data from the phase 1 and phase 2 studies for 108 patients treated with axicabtagene ciloleucel, with a median follow-up of 15.4 months. The objective response rate was 82%, and the complete response rate was 58%. Most importantly, 42% of patients were in an ongoing response at the time of the

data cut-off, with a complete response maintained in 40% of patients.

The long-term analysis of ZUMA-1 demonstrated that axicabtagene ciloleucel can lead to long-term ongoing remissions in patients with high-risk, poor-prognosis, refractory large-cell lymphoma.^{1,4} Key covariates did not predict for or against a response, including age older than 65 years, disease stage of 3 or 4, International Prognostic Index score of 3 or 4, germinal center B-cell–like disease or activated B-cell–like cell of origin, and previous use of tocilizumab or corticosteroids. Among patients with a complete response, the median duration of response was not met. Some of the patients treated in the phase 1 portion had ongoing complete responses at 24 months.

Most patients in the trial developed hypogammaglobulinemia and B-cell aplasia. Since the presentation of the primary analysis,² there have been no new reports of cytokine release syndrome, neurologic events, or grade 5 adverse events related to axicabtagene ciloleucel. Eight patients developed new-onset, treatment-emergent, serious infections, such as pneumonia and sepsis. Some patients were hospitalized, but the infections were treatable and not fatal. Biopsies at the time of

progression were available for central review in 21 patients. Immunohistochemistry showed that 33% of the biopsies were negative for CD19, suggesting that CD19-negative disease may be a mechanism of resistance or relapse.

Dr Locke also presented the interim phase 1 results from the phase 1/2 ZUMA-6 trial (A Study Evaluating KTE-C19 in Combination With Atezolizumab in Subjects With Refractory Diffuse Large B-Cell Lymphoma [DLBCL]), which evaluated axicabtagene ciloleucel in combination with atezolizumab in patients with refractory DLBCL.⁵ In this trial, the anti-programmed death ligand 1 antibody atezolizumab was administered in combination with axicabtagene ciloleucel for refractory DLBCL, as defined in the ZUMA-1 trial. Nine total patients were treated in 3 cohorts, with decreasing time from the date of infusion of CAR T cells until the initiation of atezolizumab in each cohort. The first 3 patients in cohort 1 received atezolizumab starting on day 21 after CAR T-cell therapy. The next 3 patients, in cohort 2, received atezolizumab on day 14 after administration of CAR T-cell therapy, and the third cohort received the first infusion of atezolizumab on day 1. The goal was to administer 4 doses of atezolizumab to all patients.

In general, the toxicities were comparable to those seen in ZUMA-1.² One dose-limiting toxicity occurred, in the third cohort. (Additional patients are being enrolled into this cohort.) Early evidence suggested that the combination might increase the number of CAR T cells detectable in the peripheral blood, both within the first 28 days after the CAR T-cell therapy infusion and afterward, suggesting that atezolizumab might impact CAR T-cell proliferation or persistence.

In this early analysis, the complete response rate was 56%. The overall response rate was 89%, mirroring the ZUMA-1 experience. Among the 9 patients, 2 experienced a late conver-

sion from a partial response to a complete response. The serum cytokines were comparable among patients in the phase 1 portion of ZUMA-6 as compared with those in ZUMA-1.

Dr Locke also presented a study on the use of prophylactic tocilizumab to decrease toxicity in patients treated with axicabtagene ciloleucel.⁶ This study followed the same enrollment criteria as the pivotal portion of ZUMA-1. Patients were given prophylaxis with the anti-interleukin-6 receptor antibody tocilizumab at day 2 after infusion of CAR T cells. On the day of the axicabtagene ciloleucel infusion, patients were treated with prophylactic levetiracetam to prevent seizures and neurologic toxicity. All patients underwent paired lumbar punctures at baseline and 5 days after infusion of CAR T cells, to allow comparison of cerebral spinal fluid from those who had developed neurologic toxicity vs those who did not.

The use of prophylactic tocilizumab appeared to reduce the rates of severe cytokine release syndrome. Grade 3/4 cytokine release syndrome was seen in 13% of patients in the ZUMA-1 trial, compared with 3% (1 of 34 patients) in the safety management series. However, the therapy did not reduce the incidence of severe neurologic events. In the ZUMA-1 primary analysis, 28% of patients developed grade 3 or 4 neurologic toxicity compared with 41% (14 of 34) in the safety management series. One patient experienced a grade 5 neurologic event: cerebral edema leading to death.

Importantly, the study evaluated key serum and cerebrospinal fluid biomarkers. There was no difference in CAR T-cell levels between patients in the safety management series vs those in ZUMA-1. Overall, the serum cytokine levels were similar to those in ZUMA-1, except for an increase in interleukin-6 among patients in the safety management series.

Another interesting finding was that in patients who later developed

severe grade 3 neurologic toxicity, a lumbar puncture at day 5 showed a 17-fold higher myeloid cell level and a higher CD4-to-CD8 CAR T-cell ratio in the cerebrospinal fluid as compared with patients who did not go on to develop severe neurologic toxicity.

The presentation included a case report on the patient who developed cerebral edema. This patient had new-onset B symptoms and rapid disease progression when beginning treatment with CAR T-cell therapy. At the time of pretreatment, this patient had extremely high cytokines and chemokines in the peripheral blood as compared with the other patients enrolled into the safety management series. Similar to findings in the ZUMA-1 phase 1 analysis, this again shows that patients who are in a proinflammatory state when CAR T-cell therapy is initiated are at risk for severe fatal toxicity.⁷

Tisagenlecleucel

Results from several other pivotal trials for DLBCL were presented at the 2017 ASH meeting. Tisagenlecleucel is an anti-CD19 CAR T-cell therapy with a 4-1BB costimulatory domain that is now approved by the US Food and Drug Administration for children and young adults up to age 25 years with acute lymphoblastic leukemia (ALL). The JULIET trial (Study of Efficacy and Safety of CTL019 in Adult DLBCL Patients) tested tisagenlecleucel in patients with DLBCL.⁸ Dr Stephen Schuster presented updated results from the primary analysis of the pivotal trial.⁹ An infusion of tisagenlecleucel was given to 99 patients, 80% with DLBCL and 19% with transformed follicular lymphoma. Approximately 15% of patients had double-hit or triple-hit lymphoma. There was a nearly even split between germinal center, B-cell type lymphoma (52%) and non-germinal center B-cell type lymphoma (42%).

Patients were heavily pretreated: 20% had received at least 4 lines of therapy, and 30% had received at least 3 lines. Just over half (52%) of

patients were refractory to their last line of therapy. Approximately half had undergone autologous transplant. These patient characteristics are comparable, although not identical, to the ZUMA-1 demographics.

The objective response rate was 53%, with a 40% rate of complete response, among the 81 patients with the opportunity to achieve at least 3 months of follow-up. At 3 months, 38% of patients had a complete response or partial response. Among the 46 patients who were evaluable at 6 months, 37% were in a response, with an ongoing complete response rate of 30%. The ongoing response rate of nearly 40% was similar to that seen in the ZUMA-1 trial (42%), but the follow-up was much shorter (6 months vs 15.4 months). It remains to be seen whether these responses will remain durable over a longer period. Another important aspect is the adverse event profile. Cytokine release syndrome was seen in 58% of the 99 patients, and 23% developed grade 3 or 4 cytokine release syndrome. Neurologic events were seen in 21% of patients; in 12%, these events were grade 3 or 4. There were no deaths from the use of tisagenlecleucel, cytokine release syndrome, or cerebral edema.

An important aspect to this trial is that a quarter of the patients received the infusion on an outpatient basis. In the ZUMA-1 trial with axicabtagene ciloleucel, all patients were treated as inpatients.² In the JULIET trial, among the 26 patients treated as outpatients, 77% remained an outpatient for more than 3 days after the infusion.⁹ Patients treated as outpatients likely received care at high-volume transplant centers with intensive outpatient therapy programs. Outpatient administration was possible owing to the time of onset of cytokine release syndrome. In the JULIET trial, the median time to onset was 3 days, with a range of 1 to 9 days. The timing of the onset of cytokine release syndrome may differ among the anti-CD19 CAR T-cell therapies, as well as in patients

with different diseases (eg, DLBCL vs ALL). In the JULIET trial, use of tocilizumab and corticosteroids was lower than in ZUMA-1 (15% vs 43%, and 11% vs 27%). These differences suggest that the side effect profile may differ between the therapies, although management protocols may have also been dissimilar.

The median duration of response and overall survival were not reached. The adverse events were effectively managed. It is also important to note that early in the trial, the time to manufacture the CAR T cells was long in some cases. By the end of the trial, the manufacturing time was approximately 22 days.

JCAR017

The TRANSCEND trial (Study Evaluating the Safety and Pharmacokinetics of JCAR017 in B-Cell Non-Hodgkin Lymphoma) evaluated JCAR017, an anti-CD19 CAR T-cell therapy with a 4-1BB costimulatory domain, in patients with B-cell lymphoma.¹⁰ There were 2 patient cohorts in the trial, one for DLBCL and one for mantle cell lymphoma. The presentation at the 2017 ASH meeting focused on patients with DLBCL.¹¹ These patients had transformed follicular lymphoma and prior mediastinal B-cell lymphoma, after 2 lines of therapy. Leukapheresis was performed in 140 patients. At the time of the presentation, 108 DLBCL patients had received therapy with JCAR017, and 91 were evaluable for safety. The trial evaluated different doses. Among the 91 patients who were evaluable in the full cohort, the median age was 61 years, and 37% were ages 65 years or older. DLBCL was de novo in 65% and transformed from follicular lymphoma in 21%. Twenty percent of patients had double-hit or triple-hit lymphoma, and 67% were chemorefractory and had stable disease or progressive disease after their previous line of chemotherapy or had progressed within 12 months of undergoing an autologous transplant. This distinction is important because it

suggests that only 67% of the patients treated in TRANSCEND would have potentially been eligible for ZUMA-1.

Among the evaluable patients, 35% developed cytokine release syndrome, which was grade 3/4 in only 1%. Neurologic toxicity was seen in 19% of patients, and 12% of these events were grade 3 or 4. There were no deaths from cytokine release syndrome or neurologic toxicity. The median time to onset of cytokine release syndrome was 5 days, with a range of 1 to 14. Median time to neurologic toxicity was 10 days, with a range of 3 to 23. Twelve percent of patients received tocilizumab, and 16% received dexamethasone.

In the full cohort, 74% of patients responded, and 52% had a complete response. At the 3-month time point, 72 patients were evaluable, and 53% remained in response. At the 6-month time point, 54 patients were evaluable, and 35% remained in response. These response outcomes were similar to those in the ZUMA-1 and JULIET trials.^{2,9} In TRANSCEND, 35% of patients remained in remission at 6 months.¹¹ The overall survival for patients with a complete response had not been reached at the time of the analysis.

Other Therapies for Aggressive Lymphoma

Rituximab

Dr Jacoline Bromberg presented results from the first randomized, phase 3 trial evaluating the addition of rituximab to a high-dose methotrexate-containing regimen as first-line treatment in patients with primary central nervous system lymphoma.¹² Rituximab is a large monoclonal protein with poor central nervous system penetration, and its efficacy in primary central nervous system lymphoma is controversial. Previously, the evidence supporting rituximab for the treatment of primary central nervous system lymphoma remained limited to several retrospective analyses, however, its use

is widespread and supported by efficacy in relapsed and disseminated disease.¹³ Data from a more recent phase 2 study and a large retrospective analysis have been less robust.^{14,15} This phase 3 study enrolled 100 patients in each arm. It was an international study, conducted in the Netherlands, Australia, and New Zealand. Rituximab was given in 6 doses of 375 mg/m² in combination with 2 cycles of a high-dose methotrexate-containing regimen (MBVP) and 1 cycle of high-dose ara-C as consolidation. Patients younger than 60 years also received radiation. The arms were well-balanced in terms of age and performance status as assessed by criteria from the World Health Organization and Memorial Sloan Kettering Cancer Center. The primary endpoint was event-free survival, and overall survival was a secondary outcome.

Disappointingly, although not completely surprisingly, the response was the same in both arms, at 87%. At 1 year, the event-free survival was nearly the same in both arms, at 52% with rituximab vs 49% without. The overall survival data are not yet mature, but there does not appear to be a large difference between the arms. A multivariate analysis showed a potential benefit with the addition of rituximab among patients younger than 60 years. Among these patients, the event-free survival was improved with rituximab, showing a nearly significant *P* value of .054 and a hazard ratio close to 0.5. The biological explanation for this marginal benefit is unclear. This trend was not reported in patients older than 60 years.

Rituximab may improve outcome in younger patients. However, a dedicated prospective study in this population is warranted for confirmation. For now, results from this phase 3 study definitely contradict standard practices that have been based on weaker levels of evidence. Guidelines such as those from the National Comprehensive Cancer Network recommend the addition of rituximab in the upfront setting

for patients with primary central nervous system lymphoma. This abstract puts into question these recommendations, and furthers our belief that the addition of rituximab in this setting should be limited to prospective trials.

ADCT-402

Dr Brad Kahl presented results from a phase 1 trial of ADCT-402, a new CD19 monoclonal antibody drug conjugate, in patients with relapsed/refractory B-cell refractory non-Hodgkin lymphoma.¹⁶ This study enrolled 80 patients and followed a 3 + 3 dose-escalation design. The patients' median age was 65 years, and their median number of prior therapies was 3. Most of the patients (95%) had DLBCL, but other diagnoses included mantle cell lymphoma, follicular lymphoma, marginal zone lymphoma, and chronic lymphocytic leukemia.

The treatment was relatively well-tolerated. One patient developed a dose-limiting toxicity, which was severe thrombocytopenia that occurred at the maximum dose of 200 µg/kg. The maximum tolerated dose was not reached and could not be estimated. More than 50% of patients experienced grade 3 toxicity. The most common grade 3 or higher adverse event was neutropenia. Transaminitis, anemia, fatigue, and thrombocytopenia were also reported.

At doses above 120 µg/kg, the complete response rate was 35% and the partial response rate was 25%, for an overall response rate of 60%. These response rates are very positive, but long-term data regarding durability are not yet available.

ADCT-402 is another therapy that targets CD19, along with the current CAR T-cell therapies. In addition, the CD19 monoclonal antibody blinatumomab has been tested in phase 2 trials.^{17,18} Blinatumomab is approved for ALL. Although cross-trial comparison is tricky, the phase 1 data for ADCT-402 showed better overall response rates and complete response

rates than the phase 2 data for blinatumomab, and ADCT-402 was better tolerated. However, other questions arise regarding the use of these different types of CD19-targeted therapies. Will patients treated with ADCT-402 or blinatumomab remain good candidates for CAR T-cell therapy, or might they lose expression of CD19? It may be that ADCT-402 will be preferred in certain settings, such as in patients who are not eligible for CAR T-cell therapy, patients in whom it is not possible to engineer CAR T cells, or patients in whom it would be prudent to avoid any delay in treatment that might result from the manufacturing process of the CAR T cell product. It is possible that CD19 loss may be a mechanism of escape, and using ADCT-402 in sequence with CD19 CAR T-cell therapy may alter patients' response rates. Patients treated with ADCT-402 may still be candidates for CAR T-cell therapy, especially if they maintain CD19 positivity. However, prior use of ADCT-402 may decrease the response rates to CAR T-cell therapy. Nevertheless, this is a very exciting novel therapy, especially if subsequent trials show durability of response rates.

R-GCVP

Dr Betty Gration presented results of a study of R-GCVP as second-line treatment of elderly patients with DLBCL who required therapy after cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and were not candidates for intensive therapy.¹⁹ This retrospective study evaluated data for 24 patients with relapsed or refractory DLBCL from 3 hospitals in London. Elderly patients are a significant component of the DLBCL population. In the frontline setting, there are good response rates, higher than 50%, with rituximab-CHOP (R-CHOP) mini and the standard R-CHOP regimen. When patients cannot tolerate an anthracycline, they are often treated with rituximab plus cyclophosphamide, vincristine, and prednisone

(R-COP), with or without etoposide. Treatment for the second-line setting is less clear. Patients may be ineligible for intensive management with high-dose chemotherapy and autologous transplant. In this retrospective study, 18 of 24 patients had de novo DLBCL, and 6 patients had DLBCL that transformed from indolent non-Hodgkin lymphoma. The median age was 77, and the median Eastern Cooperative Oncology Group performance status was 2. Most patients had at least 1 significant comorbidity. Nearly all patients (23 of 24) had received a regimen containing anthracycline, either R-CHOP or R-CHOP mini. All patients had received prior rituximab. Only 1 patient had undergone prior autologous stem cell transplant.

The analysis showed a complete response in 10 of the patients and a partial response in another 10, for an overall response in 20 patients. The median overall survival was 11 months, and the disease-free survival reached a median of approximately 8 months. Among the 20 patients who died, the death was attributed to lymphoma progression in 18. Progressive disease is still the major morbidity and mortality in this elderly group of patients with comorbidities. More active and well-tolerated regimens should be studied and compared in this population of patients, who are not candidates for hematopoietic stem cell transplant. Among patients with relapsed or refractory disease who have a poor prognosis, possible alternative regimens include rituximab plus cyclophosphamide, etoposide, vincristine and prednisone (R-CEOP); bendamustine plus rituximab; gemcitabine plus oxaliplatin; lenalidomide plus rituximab; and, possibly, adoptive T-cell therapies, such as CAR T cells. In the retrospective analysis of R-GCVP 71% of patients required hospitalization, most often because of infection, despite prophylaxis with granulocyte colony-stimulating factor. Patients with relapsed or refractory

DLBCL that had transformed tend to respond better to R-GCVP than patients with de novo relapsed or refractory DLBCL. R-GCVP might be an option in elderly patients who relapse after a long duration of disease-free survival after initial therapy or in elderly patients without a large burden of disease. However, the use of R-GCVP is harder to justify in patients with significant disease burden or refractory disease. This regimen was not particularly well-tolerated, nor did it achieve the desired long-term overall survival rates. Accordingly, the search should continue for more effective and well-tolerated treatments for this population.

Disclosures

Dr Locke has served as a scientific advisor to Kite Pharma and as a consultant to Cellular Biomedicine Group Inc. Dr Haroun is providing ad-hoc consultant services for AstraZeneca for medical review of training materials and other medical activities through March 18, 2018.

References

1. Neelapu SS, Locke FL, Bartlett NL, et al. Long-term follow-up ZUMA-1: a pivotal trial of axicabtagene ciloleucel (axi-cel; KTE-C19) in patients with refractory aggressive non-Hodgkin lymphoma (NHL) [ASH abstract 578]. *Blood*. 2017;130(suppl 1).
2. Locke FL, Neelapu SS, Bartlett NL, et al. Primary results from ZUMA-1: a pivotal trial of axicabtagene ciloleucel (axicel; KTE-C19) in patients with refractory aggressive non-Hodgkin lymphoma (NHL) [AACR abstract CT019]. Presented at: Annual Meeting of the American Association for Cancer Research; April 1-5, 2017; Washington, DC.
3. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood*. 2017;130(16):1800-1808.
4. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med*. 2017;377(26):2531-2544.
5. Locke FL, Westin JR, Miklos DB, et al. Phase 1 results from ZUMA-6: axicabtagene ciloleucel (axi-cel; KTE-c19) in combination with atezolizumab for the treatment of patients with refractory diffuse large B cell lymphoma (DLBCL) [ASH abstract 2826]. *Blood*. 2017;130(suppl 1).
6. Locke FL, Neelapu SS, Bartlett NL, et al. Preliminary results of prophylactic tocilizumab after axicabtagene ciloleucel (axi-cel; KTE-C19) treatment for patients with refractory, aggressive non-Hodgkin lymphoma

- [ASH abstract 1547]. *Blood*. 2017;130(suppl 1).
7. Locke FL, Neelapu SS, Bartlett N, et al. Phase 1 results of ZUMA-1: a multicenter study of KTE-C19 anti-CD19 CAR T cell therapy in refractory aggressive lymphoma. *Mol Ther*. 2017;25(1):285-295.
8. Schuster SJ, Bishop MR, Tam C, et al. Global pivotal phase 2 trial of the CD19-targeted therapy cdl019 in adult patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL)—an interim analysis [ICML abstract 007]. *Hematol Oncol*. 2017;35(suppl s2).
9. Schuster SJ, Bishop MR, Tam CS, et al. Primary analysis of JULIET: a global, pivotal, phase 2 trial of CTL019 in adult patients with relapsed or refractory diffuse large B-cell lymphoma [ASH abstract 577]. *Blood*. 2017;130(suppl 1).
10. Abramson JS, Palomba ML, Gordon L, et al. High CR rates in relapsed/refractory (R/R) aggressive B-NHL treated with the CD19-directed CAR T cell product JCAR017 (TRANSCEND NHL 001) [ICML abstract 128]. *Hematol Oncol*. 2017;35(suppl s2).
11. Abramson JS, Palomba ML, Gordon LI, et al. High durable CR rates in relapsed/refractory (r/r) aggressive B-NHL treated with the CD19-directed CAR T cell product JCAR017 (TRANSCEND NHL 001): defined composition allows for dose-finding and definition of pivotal cohort [ASH abstract 581]. *Blood*. 2017;130(suppl 1).
12. Bromberg J, Issa S, Bukanina K, et al. Effect of rituximab in primary central nervous system lymphoma—results of the randomized phase III HOVON 105/ALLG NHL 24 study [ASH abstract 582]. *Blood*. 2017;130(suppl 1).
13. Holdhoff M, Ambady P, Abdelaziz A, et al. High-dose methotrexate with or without rituximab in newly diagnosed primary CNS lymphoma. *Neurology*. 2014;83(3):235-239.
14. Ferreri AJ, Cwynarski K, Pulczynski E, et al; International Extranodal Lymphoma Study Group (IELSG). Chemoimmunotherapy with methotrexate, cytarabine, thiopeta, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomisation of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial. *Lancet Haematol*. 2016;3(5):e217-e227.
15. Mocikova H, Pytlík R, Sykorova A; Czech Lymphoma Study Group. Role of rituximab in treatment of patients with primary central nervous system lymphoma: a retrospective analysis of the Czech lymphoma study group registry. *Leuk Lymphoma*. 2016;57(12):2777-2783.
16. Kahl BS, Hamadani M, Caimi P, et al. Encouraging early results from the first in-human clinical trial of ADCT-402 (loncastuximab tesirine), a novel pyrrolbenzodiazepine-based antibody drug conjugate, in relapsed/refractory B-cell lineage non-Hodgkin lymphoma [ASH abstract 187]. *Blood*. 2017;130(suppl 1).
17. Viardot A, Goebeler ME, Hess G, et al. Phase 2 study of the bispecific T-cell engager (BiTE) antibody blinatumomab in relapsed/refractory diffuse large B-cell lymphoma. *Blood*. 2016;127(11):1410-1416.
18. Goebeler ME, Knop S, Viardot A, et al. Bispecific T-cell engager (BiTE) antibody construct blinatumomab for the treatment of patients with relapsed/refractory non-Hodgkin lymphoma: final results from a phase I study. *J Clin Oncol*. 2016;34(10):1104-1111.
19. Gration B, Duran A, Mir N, et al. R-GCVP as second line treatment in elderly patients with DLBCL who fail R-CHOP and are not candidates for intensive therapy [ASH abstract 4133]. *Blood*. 2017;130(suppl 1).

