

A SPECIAL MEETING REVIEW EDITION

**Advances in Aggressive Lymphoma From the 2018
American Society of Clinical Oncology Annual Meeting**

A Review of Selected Presentations From the 2018 American Society of Clinical
Oncology Annual Meeting • June 1-5, 2018 • Chicago, Illinois

Special Reporting on:

- Durability of Response in ZUMA-1, the Pivotal Phase 2 Study of Axicabtagene Ciloleucel in Patients With Refractory Large B-Cell Lymphoma
- Updated Safety and Long-Term Clinical Outcomes in TRANSCEND NHL 001, Pivotal Trial of Lisocabtagene Maraleucel (JCAR017) in R/R Aggressive NHL
- Outcomes by Prior Lines of Therapy in ZUMA-1, the Pivotal Phase 2 Study of Axicabtagene Ciloleucel in Patients With Refractory Large B-Cell Lymphoma
- Factors Associated With Duration of Response After CD-Specific CAR-T Cell Therapy for Refractory/Relapsed B-Cell Non-Hodgkin Lymphoma
- Randomized Phase 2 Trial of Polatuzumab Vedotin With Bendamustine and Rituximab in Relapsed/Refractory FL and DLBCL
- Radiotherapy to Bulky and Extralymphatic Disease in Combination With 6×R-CHOP-14 or R-CHOP-21 in Young Good-Prognosis DLBCL Patients: Results of the 2×2 Randomized UNFOLDER Trial of the DSHNHL/GLA
- Phase I/II Clinical Trial of Ibrutinib and Buparlisib in Relapsed/Refractory Diffuse Large B-Cell Lymphoma, Mantle Cell Lymphoma, and Follicular Lymphoma
- Dose-Adjusted-EPOCH-R With High-Dose Methotrexate for Newly Diagnosed Stage II-IV CD5-Positive Diffuse Large B-Cell Lymphoma: Primary Analysis of the PEARL5 Study

PLUS Meeting Abstract Summaries

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ON THE WEB:
hematologyandoncology.net

YES CAR T IS HERE

YESCARTA®, THE FIRST CAR T THERAPY FOR CERTAIN TYPES OF RELAPSED OR REFRACTORY LARGE B-CELL LYMPHOMA

The following data reflect results from the ZUMA-1 pivotal trial*¹

// PROVEN EFFICACY

51%

Patients achieved a best response of complete remission (CR) (52/101)

NR

Response duration was not reached at a median follow-up of 7.9 months in patients who achieved CR

// CYTOKINE RELEASE SYNDROME

13% 94%

Grade ≥ 3 incidence Overall incidence

// NEUROLOGIC TOXICITIES

31% 87%

Grade ≥ 3 incidence Overall incidence

// RAPID & RELIABLE MANUFACTURING

17 DAYS

Median turnaround time[†]

99%

Manufacturing success of CAR T cells engineered and expanded ex vivo

VISIT YESCARTAHCP.COM/CENTERS TO FIND A LIST OF AUTHORIZED TREATMENT CENTERS

*ZUMA-1 was an open-label, single-arm study in 101 adult patients who received YESCARTA® therapy. Patients received lymphodepleting chemotherapy prior to a single infusion of YESCARTA® at a target dose of 2×10^6 viable CAR T cells/kg body weight (maximum of 2×10^8 viable CAR T cells). Patients had refractory disease to their most recent therapy, or had relapsed within 1 year after autologous hematopoietic stem cell transplantation.

[†]The median time from leukapheresis to product delivery.

INDICATION

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

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

IMPORTANT SAFETY INFORMATION

BOXED WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGIC TOXICITIES

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

Important Safety Information continued on adjacent page.

IMPORTANT SAFETY INFORMATION (continued)

CYTOKINE RELEASE SYNDROME (CRS): CRS occurred in 94% of patients, including 13% with \geq Grade 3. Among patients who died after receiving YESCARTA[®], 4 had ongoing CRS at death. The median time to onset was 2 days (range: 1-12 days) and median duration was 7 days (range: 2-58 days). Key manifestations include fever (78%), hypotension (41%), tachycardia (28%), hypoxia (22%), and chills (20%). Serious events that may be associated with CRS include cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome. Ensure that 2 doses of tocilizumab are available prior to infusion of YESCARTA[®]. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for 4 weeks after infusion. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time. At the first sign of CRS, institute treatment with supportive care, tocilizumab or tocilizumab and corticosteroids as indicated.

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

YESCARTA[®] REMS: Because of the risk of CRS and neurologic toxicities, YESCARTA[®] is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA[®] REMS. The required components of the YESCARTA[®] REMS are: Healthcare facilities that dispense and administer YESCARTA[®] must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of 2 doses of tocilizumab are available for each patient for infusion within 2 hours after YESCARTA[®] infusion, if needed for treatment of CRS. Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer YESCARTA[®] are trained about the management of CRS and neurologic toxicities. Further information is available at www.YESCARTAREMS.com or 1-844-454-KITE (5483).

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

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

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

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

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

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

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

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

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

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITIES

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

1 INDICATIONS AND USAGE

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

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

2 DOSAGE AND ADMINISTRATION

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

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

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

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

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

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

2.3 Management of Severe Adverse Reactions

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

Table 1. CRS Grading and Management Guidance

CRS Grade (a)	Tocilizumab	Corticosteroids
Grade 1 Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).	N/A	N/A
Grade 2 Symptoms require and respond to moderate intervention. Oxygen requirement less than 40% FiO ₂ or hypotension responsive to fluids or low-dose of one vasopressor or Grade 2 organ toxicity (b).	Administer tocilizumab (c) 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). 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)].

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Durability of Response in ZUMA-1, the Pivotal Phase 2 Study of Axicabtagene Ciloleucel in Patients With Refractory Large B-Cell Lymphoma

Axicabtagene ciloleucel is an autologous chimeric antigen receptor (CAR) therapy that is designed to reinstate T-cell activation by allowing a patient's genetically engineered T cells to recognize CD19, a cell surface marker that is expressed on the vast majority of B-cell malignancies.¹ The axicabtagene ciloleucel CAR molecule consists of an antibody variable domain, a transmembrane region, and the CD28 and CD3 ζ domains, which signal T-cell activation. The construct enables recognition of CD19 that induces T-cell activation and proliferation, as well as activation of inflammatory pathways that result in tumor cell lysis.

The phase 1/2 ZUMA-1 trial (A Phase 1-2 Multi-Center Study Evaluating Axicabtagene Ciloleucel in Subjects With Refractory Aggressive Non-Hodgkin Lymphoma) evaluated axicabtagene ciloleucel therapy in patients with refractory, aggressive B-cell non-Hodgkin lymphoma (NHL).² The trial met its primary endpoint after the primary analysis, which led to the approval of axicabtagene ciloleucel 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 The trial enrolled patients with refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), and transformed follicular lymphoma. Patients had not responded to their most recent line of chemotherapy or had relapsed within 12 months after autologous hematopoietic stem cell transplant (SCT). After leukapheresis and manufacture of axicabtagene ciloleucel, patients received treatment with a low-dose conditioning chemotherapy regimen

that consisted of fludarabine (30 mg/m² daily) and cyclophosphamide (500 mg/m² daily) on days -5, -4, and -3 before administration of axicabtagene ciloleucel. Axicabtagene ciloleucel was administered via a single intravenous infusion at a target dose of 2×10^6 CAR T cells/kg on day 0. Patients who demonstrated an initial response followed by disease progression at least 3 months after the initial dose of axicabtagene ciloleucel were re-treated. The primary endpoint was the investigator-assessed objective response rate (ORR) according to the International Working Group Response Criteria for Malignant Lymphoma.⁴ Cytokine release syndrome was graded according to published recommendations.⁵ Adverse events (AEs), including symptoms of cytokine release syndrome, were graded based on the National Cancer Institute Common Terminology Cri-

teria for Adverse Events, version 4.03.

The overall analysis of ZUMA-1 showed an ORR of 82%, with a complete response (CR) rate of 54%. At a median follow-up of 15.4 months, the ORR was 42%, and the CR was 40%. The overall rate of survival was 52% at 18 months.²

Dr Frederick Locke presented results of long-term follow-up, which was available for 108 patients, including 7 patients from phase 1 and 101 patients from phase 2.⁶ In the phase 1 portion, the 7 patients had refractory DLBCL, PMBCL, or transformed follicular lymphoma. In the phase 2 trial, 77 patients with DLBCL and 24 patients with PMBCL or transformed follicular lymphoma were enrolled into separate cohorts. The data cutoff was August 11, 2017. The median follow-up was 15.4 months, and the minimum was 12 months. Axicabtagene ciloleucel manufacture was successful

ABSTRACT SUMMARY The Social Value of Tisagenlecleucel, a CAR-T Cell Therapy, for the Treatment of Relapsed or Refractory Pediatric Acute Lymphoblastic Leukemia in the United States: What Are Consequences of Treatment Delays?

The social value of tisagenlecleucel treatment in pediatric patients with ALL in the United States was evaluated by obtaining estimates of life expectancy, quality-adjusted life years (QALYs), and health care costs (Abstract 10529). Each QALY gained was valued at \$150,000, with a tisagenlecleucel price of \$475,000. The analysis assumed that patients would receive treatment with clofarabine while awaiting treatment with tisagenlecleucel. Twenty incident cohorts included 500 pediatric patients with ALL. Patients treated with tisagenlecleucel gained 37,018 QALYs, reflecting a total social value of \$4.6 billion. However, when treatment was delayed for 1 to 3 months, a loss of 3634 to 17,100 QALYs and \$452 million to \$2.1 billion of social value was incurred. When treatment was delayed by 4 months, over half of the social value, value to patients, and QALYs from tisagenlecleucel was lost. Treatment delays may be minimized by the development of efficient payment mechanisms and technologic resources.

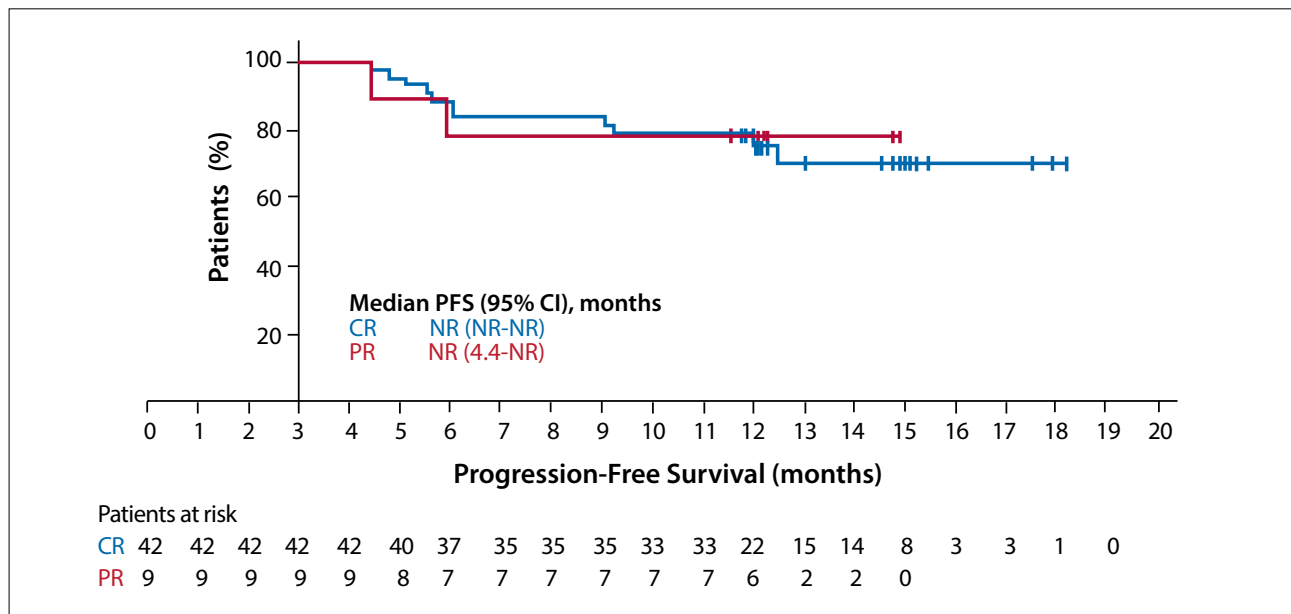


Figure 1. Progression-free survival according to response at month 3 in the ZUMA-1 trial of axicabtagene ciloleucel. CR, complete response; NR, not reached; PFS, progression-free survival; PR, partial response; ZUMA-1, A Phase 1-2 Multi-Center Study Evaluating Axicabtagene Ciloleucel in Subjects With Refractory Aggressive Non-Hodgkin Lymphoma. Adapted from Locke FL et al. ASCO abstract 3003. *J Clin Oncol.* 2018;36(15 suppl).⁶

in 99% of enrolled patients, and 91% of patients received an infusion of genetically engineered CAR T cells.

With long-term follow-up, the ORR was 82%, and included a CR rate of 58%. Ongoing responses were observed in 42% of patients, and most consisted of CRs. Median overall survival (OS) was not reached, and 12-month OS was 60%. These results compare favorably with data from historical controls in a similar patient population, which show that the ORR reaches 25% after another line of salvage therapy. Twelve percent of patients in the phase 1/2 population experienced cytokine release syndrome of grade 3 or higher, and 31% had a neurologic AE of at least grade 3. The median duration of response was 11.1 months overall (95% CI, 3.9 months to not reached), not reached among patients with a CR (95% CI, not reached to not reached), and 1.9 months (1.4-2.1 months) among those with a partial response (PR).

Among the patients who achieved a CR, one-third initially exhibited a PR, and that response deepened

over time. Among patients who progressed, more than half progressed by 3 months after treatment, underscoring month 3 as a clinically important time to evaluate the potential need for any further treatment. As a result, a main objective of the long-term analysis was to evaluate the time to response, including CRs, and to assess PR and CR at month 3 posttreatment as a prognostic factor for progression-free survival (PFS; Figure 1). Among the 44 patients who initially experienced a PR, 18 patients (41%) eventually exhibited a CR (Figure 2). The median time to response was 1 month (range, 0.8-14.8 months) in the overall population and 1 month (range, 0.8-12.3 months) among patients with a CR. Kaplan-Meier analysis of ORR and CR over time showed an inflection point at month 3, reflecting the deepening response in some patients with a CR. Although many conversions from a PR to a CR were seen at 3 months after the axicabtagene ciloleucel treatment, some patients with an initial PR did not develop a CR until

as late as 12 months after the single infusion of CAR T-cell therapy.

Baseline characteristics were generally similar in patients who achieved a PR vs a CR at 3 months, as well as in the overall phase 2 population of 101 patients. In the overall population, the median age was 58 years (range, 23-76 years), and 85% had stage III/IV disease. Forty-six percent of patients had an International Prognostic Index (IPI) score of 3 to 4, and 69% had received 3 or more prior therapies. PFS at month 3 was not reached in patients who achieved a CR (95% CI, not reached to not reached) or PR (95% CI, 4.4 months to not reached). The Kaplan-Meier curves for the 2 response cohorts were similar and crossed over after approximately 9 months. For the small number of patients with stable disease at month 3, 44% remained in response at 12 months after the axicabtagene ciloleucel infusion.

Patients with a response at month 3 were likely to remain in response at month 12. For the 9 patients with a PR at month 3, 78% (95% CI, 36%-94%) remained in PR at month

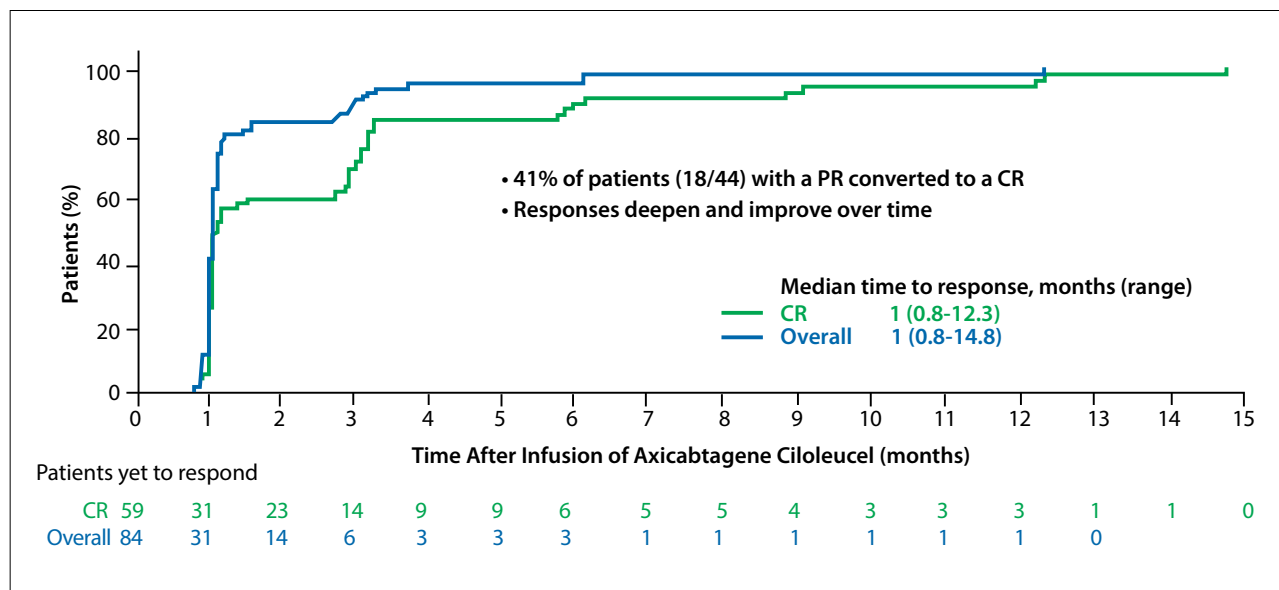


Figure 2. Time to objective response and complete response in the ZUMA-1 trial of axicabtagene ciloleuceL. CR, complete response; PR, partial response; ZUMA-1, A Phase 1-2 Multi-Center Study Evaluating Axicabtagene CiloleuceL in Subjects With Refractory Aggressive Non-Hodgkin Lymphoma. Adapted from Locke FL et al. ASCO abstract 3003. *J Clin Oncol.* 2018;36(15 suppl).⁶

12. Similarly, among the 42 patients with a CR at month 3 after treatment, 79% (95% CI, 63%-88%) maintained the response at month 12. Based on this analysis, watchful waiting is the preferred approach for patients who exhibit a CR or PR at 3 months.

Similar rates of cytokine release syndrome and neurologic events were observed across all response groups and in the overall study population. In the phase 2 population of 101 patients, 100% of patients with a PR and 93% of those with a CR experienced an AE of grade 3 or higher. Cytokine release syndrome of grade 3 or higher was observed in no patients with a PR vs 12% of those with a CR. Neurologic

events of grade 3 or higher occurred in 33% vs 36%, respectively. Based on the ZUMA-1 experience, a multidisciplinary approach has been recommended for monitoring, grading, and managing the acute toxicities that may occur in patients who received CAR T-cell therapy.⁷ Management of toxicities may include aggressive supportive care, anti-interleukin (IL) 6 therapy, and/or corticosteroids for severe cases. Intervening when toxicities are at grade 2 may forestall advancement to higher-grade AEs.

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Updated Safety and Long-Term Clinical Outcomes in TRANSCEND NHL 001, Pivotal Trial of Lisocabtagene MaraleuceL (JCAR017) in R/R Aggressive NHL

The international, multicohort SCHOLAR-1 study (Retrospective Non-Hodgkin Lymphoma Research) retrospectively

analyzed data from 636 patients with refractory DLBCL.^{1,2} Salvage therapy yielded an ORR of 26% and a CR rate of 7%. Poor survival was more

common in patients who had never achieved a CR, had never received autologous SCT, had chemorefractory disease, or had an Eastern Cooperative

Oncology Group (ECOG) performance status of 2. Lisocabtagene maraleucel (also known as JCAR017) is a CD19-directed CAR T-cell therapy that provides a known ratio of CD4-positive and CD8-positive cells.^{3,4} In addition to having an anti-CD19 single-chain antibody variable domain, the CAR construct uses the 4-1BB co-stimulatory domain and provides intracellular T-cell signaling through CD3 ζ . After leukapheresis, the patient's CD4-positive cells are separated from CD8-positive cells. These T-cell populations then undergo transduction with a lentivirus vector that expresses the CAR construct, followed by expansion.

The TRANSCEND NHL 001 trial (Study Evaluating the Safety and Pharmacokinetics of JCAR017 in B-Cell Non-Hodgkin Lymphoma) investigated 3 dose levels of lisocabtagene maraleucel in NHL patients who had received at least 2 prior lines of therapy.⁵ In the dose-finding cohorts, patients received 5×10^7 CAR T cells in a single dose (DL1S); the same total number of CAR T cells divided into 2 half-doses (DL1D); or a single dose of 1×10^8 engineered cells (DL2S). This initial study was followed by evaluation of 2 dose-expansion cohorts. The analysis included 102 patients in the full cohort and 73 in the core cohort. Patients in the core cohort had DLBCL or high-grade B-cell lymphoma. Patients in the full cohort included those in the core cohort, but patients could also have PMBCL or stage 3B follicular lymphoma. Patients in the initial cohorts had an ECOG performance status of 0 to 2, but the status was limited to 0 or 1 among patients in the pivotal cohort. There was no minimum absolute lymphocyte count required for leukapheresis. Prior SCT and central nervous system involvement were allowed. After apheresis, patients underwent 3 days of treatment for lymphodepletion with fludarabine (30 mg/m²) and cyclophosphamide (300 mg/m²). Lisocabtagene maraleucel treatment

ABSTRACT SUMMARY Randomized, Open-Label, Phase 2 Trial of Everolimus Versus Thalidomide in Patients Achieving Remission After First-Line Therapy for High-Risk Diffuse Large B-Cell Lymphoma

A single-center, open-label, randomized phase 2 trial evaluated 2 years of treatment with everolimus (5 mg daily) vs thalidomide (100-300 mg daily) as maintenance therapy in 102 patients with DLBCL. Patients had achieved a CR after first-line treatment with R-CHOP, but were at high risk for relapse (Abstract 7560). After a median follow-up of 34.2 months, 2-year disease-free survival was 84.9% with everolimus vs 84.2% with thalidomide (hazard ratio [HR], 0.958; 95% CI, 0.370-2.484), and 2-year OS was 93.4% vs 91.4%, respectively (HR, 0.711; 95% CI, 0.169-2.998). In a control group of 137 patients, 2-year disease-free survival was 62.4% and 2-year OS was 81.6%. Compared with the control group, the everolimus maintenance group showed a superior 2-year disease-free survival (HR, 0.345; 95% CI, 0.165-0.722) and OS (HR, 0.216; 95% CI, 0.067-0.701), as did the thalidomide maintenance group (HR for 2-year disease-free survival, 0.350; 95% CI, 0.174-0.706; HR for 2-year OS, 0.335; 95% CI, 0.132-0.852). Both everolimus and thalidomide were well-tolerated.

was administered 2 to 7 days later.

The trial enrolled 134 patients with DLBCL, and a CAR T-cell product was successfully manufactured for 132 of them (99%). Among these patients, 5 withdrew and 13 developed progressive disease or died. Lisocabtagene maraleucel was administered to 114 patients; however, 12 of these patients received a nonconforming lisocabtagene maraleucel product. Among 102 evaluable patients, 45 were from cohort DL1S, 6 from DL1D, and 51 from DL2S. Patient characteristics were similar in the full and core cohorts. In the full cohort of 102 patients, the median age was 61 years (range, 20-82 years) and 36% were age 65 years or older. The most common NHL subtype was de novo DLBCL not otherwise specified (62%), and 19% of patients had double-hit or triple-hit genetic mutations. Key characteristics were well-balanced between the cohorts, including chemorefractory disease (70% in the full cohort vs 67% in the core cohort), never achieved a CR (48% vs 49%), and central nervous system involvement (2% vs 1%). Both cohorts had received a median of 3 prior lines of therapy, and patients in

both cohorts had received as many as 8 prior lines of therapy.

In the full cohort, the ORR was 75% (95% CI, 65%-83%), with a CR rate of 55% (95% CI, 45%-65%). Based on imaging conducted at 6 months after CAR T-cell treatment, the ongoing ORR was 40% (95% CI, 31%-50%), with CRs in 34% (95% CI, 25%-44%; Figure 3). For all dose levels in the core cohort, the ORR was 80% (95% CI, 68%-88%), with a CR rate of 59% (95% CI, 47%-70%). A higher CR rate was observed with the higher dose level of CAR T cells (DL2S), with 6-month CR rates of 33% (95% CI, 18%-52%) in cohort DL1S vs 46% (95% CI, 30%-63%) in cohort DL2S. Therefore, the dose of 1×10^8 CAR T cells was chosen for the pivotal cohort.

In a subgroup analysis, the lowest ORR, 26.9%, was observed among patients with an IPI score of 3 to 5 (95% CI, 11.6%-47.8%). The highest ORR was 62.5%, and was seen in patients with double-hit or triple-hit mutations. Among patients with stable or progressive disease after prior therapy, the ORR was 41.2%. The median duration of response and OS were not reached for the full or the core cohort.

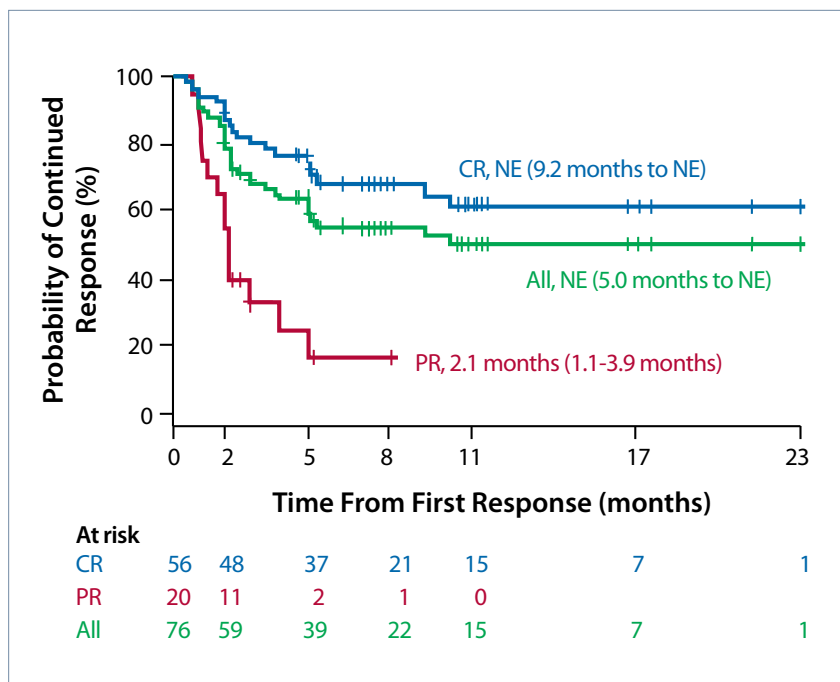


Figure 3. Durability of response in the full cohort of patients in the TRANSCEND NHL 001 trial of lisocabtagene maraleucel. CR, complete response; NE, not estimable; PR, partial response; TRANSCEND NHL 001, Study Evaluating the Safety and Pharmacokinetics of JCAR017 in B-Cell Non-Hodgkin Lymphoma. Adapted from Abramson JS et al. ASCO abstract 7505. *J Clin Oncol.* 2018;36(15 suppl).⁵

In the core cohort, 88% of patients with a CR at 3 months remained in CR at 6 months.

As anticipated, after lymphodepleting treatment, most grade 3/4 AEs consisted of cytopenias. The most

common nonhematologic AE was fatigue. In the core DLBCL population, no increase was observed in the incidence of cytokine release syndrome or neurotoxicity at the highest dose level (DL2S), and no deaths from

these AEs occurred. In the full cohort, any-grade cytokine release syndrome was observed in 37% of patients, including grade 3/4 syndrome in 1%. The median time to onset of cytokine release syndrome was 5 days (range, 2-12 days). Neurotoxicity of any grade was observed in 23% of patients in the full cohort, and included grade 3/4 events in 13%. The median time to onset of neurotoxicity was 10 days (range, 3-23 days). Serious cytokine release syndrome or neurotoxicity was observed in 13% of patients in the full cohort.

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Outcomes by Prior Lines of Therapy in ZUMA-1, the Pivotal Phase 2 Study of Axicabtagene Ciloleucel in Patients With Refractory Large B-Cell Lymphoma

To further understand the efficacy associated with axicabtagene ciloleucel in patients with refractory large B-cell lymphoma, outcomes in patients included in phases 1 and 2 of the ZUMA-1 trial were assessed by prior lines of therapy.¹⁻³ (Autologous SCT was considered a prior line of therapy.) Tumor burden was estimated by calculating the sum

of the product of the diameters (SPD) of index lesions.⁴ Analyses were conducted on patient cohorts that were defined according to the number of prior lines of therapy: 1 to 2 (cohort 1; n=32); 3 (cohort 2; n=33); 4 (cohort 3; n=30); or 5 or more (cohort 4; n=13). The proportion of patients with an IPI score of 3 to 4 increased with more lines of therapy, from one-third in

patients who received 1 to 3 lines of therapy to 69% in patients treated with 5 or more. The median SPD increased as well, from 2993 mm² (range, 180-12,795 mm²) in patients treated with 1 or 2 lines to 5106 mm² (range, 310-14,354 mm²) in those treated with 5 or more. Patients treated with 5 or more lines of therapy were also more likely to have relapsed after autologous SCT

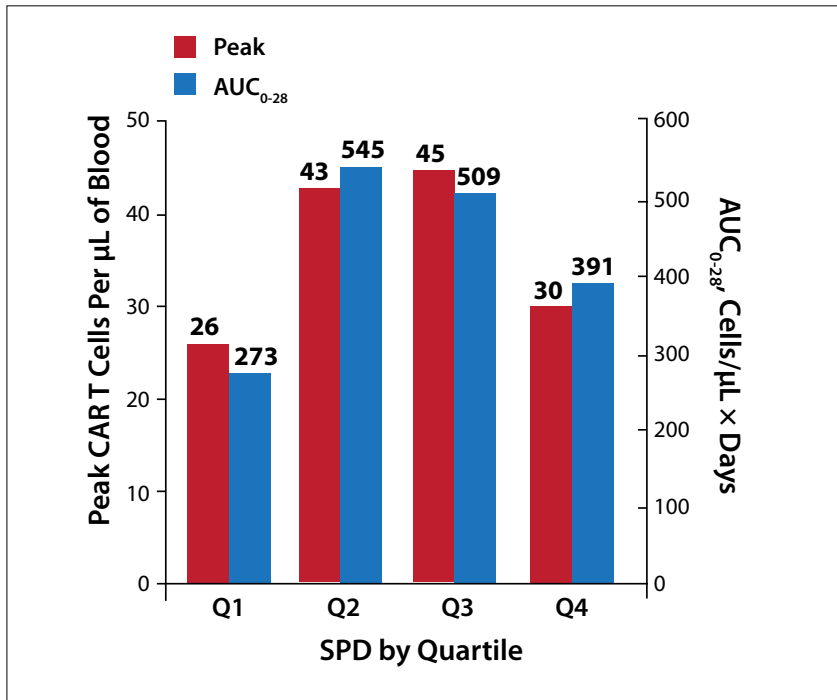


Figure 4. CAR T-cell expansion according to quartile. AUC, area under the curve; CAR, chimeric antigen receptor; Q, quartile; SPD, sum of the product of the diameters. Adapted from Locke FL et al. ASCO abstract 3039. *J Clin Oncol.* 2018;36(15 suppl).¹

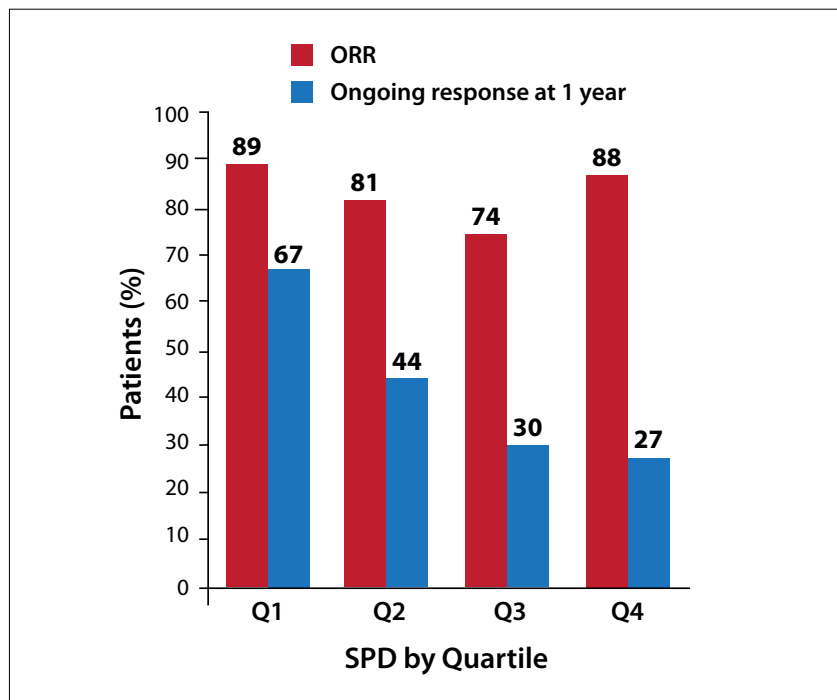


Figure 5. Objective response and response at 1 year according to quartile in the ZUMA-1 trial of axicabtagene ciloleucel. ORR, objective response rate; Q, quartile; SPD, sum of the product of the diameters; ZUMA-1, A Phase 1-2 Multi-Center Study Evaluating Axicabtagene Ciloleucel in Subjects With Refractory Aggressive Non-Hodgkin Lymphoma. Adapted from Locke FL et al. ASCO abstract 3039. *J Clin Oncol.* 2018;36(15 suppl).¹

(46% vs 0%-33% in cohorts 1-3). Among the 4 cohorts, the CAR T-cell product parameters were similar, with doubling times of 1.4 days to 1.7 days, transduction rates ranging from 50% to 60%, and a CD4-to-CD8 ratio ranging from 0.7 to 1.1.

ORRs ranged from 94% in patients treated with 3 lines to 38% in patients treated with 5 or more. Across the 4 cohorts, rates of serious AEs ranged from 23% in patients treated with 3 lines to 54% in those treated with 5 or more. Rates of cytokine release syndrome of grade 3 or higher were similar across the 4 cohorts. There was, however, a trend toward higher rates of serious AEs of grade 3 or higher and neurologic events among patients treated with 5 or more lines. Patients treated with 1 to 3 lines of therapy showed similar outcomes in terms of CAR T-cell production. The median peak number of cells/ μL ranged from 31 cells/ μL to 44 cells/ μL , and the median area under the curve ranged from 462 cells/ μL \times days to 502 cells/ μL \times days. These numbers were lower among patients treated with 5 or more lines, in whom the median peak was 20 cells/ μL and the median area under the curve was 273 cells/ μL \times days.

Patients were also divided into quartiles according to tumor burden. The median SPD was 840 mm^2 in quartile 1, 2823 mm^2 in quartile 2, 5106 mm^2 in quartile 3, and 9340 mm^2 in quartile 4 (Figure 4). The ORRs ranged from 74% in quartile 3 to 89% in quartile 1 (Figure 5). However, the proportion of patients with an ongoing response at 1 year after treatment decreased with increasing SPD, from 67% in quartile 1 to 27% in quartile 4. The proportion of patients with an IPI score of 3 to 4 was 30% in SPD quartiles 1 and 2, 63% in quartile 3, and 54% in quartile 4.

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Factors Associated With Duration of Response After CD-Specific CAR-T Cell Therapy for Refractory/Relapsed B-Cell Non-Hodgkin Lymphoma

A phase 1/2 study investigated the factors that affect disease response and related outcomes among lymphoma patients treated with CAR T-cell therapy.¹⁻³ The study included adults with relapsed or refractory, CD19-positive B-cell malignancies. As of April 20, 2017, 166 patients had been treated, including 57 with acute lymphoblastic leukemia (ALL), 30 with chronic lymphocytic leukemia,

and 79 with NHL. Dr Jordan Gauthier reported results from 57 patients included in the trial, all of whom underwent lymphodepletion followed by infusion of 2×10^6 CAR T cells at a 1-to-1 ratio of CD4-positive and CD8-positive engineered cells.⁴ Disease histology was indolent in 9 patients and aggressive in 48. The patients had a median age of 56.5 years (range, 27-71 years), and

95% had stage III/IV disease. Among the patients with indolent histology, 44% had extranodal disease, 12% had an IPI score of 3 or 4, and none had bulky disease. Among the patients with aggressive histology, 92% had extranodal disease, 52% had an IPI score of 3 or 4, and 17% had bulky disease. For the entire study population, the median number of prior lines of therapy was 4 (range, 1-11), and the median SPD was 3343 mm² (range, 124-16,765 mm²).

The ORR was 89% in patients with indolent NHL, and all responses were complete. In patients with aggressive NHL, the ORR was 53%, which included a CR rate of 38%. In the mixed population of 57 patients, those who achieved a CR had a dramatically improved median PFS compared with those who did not (24-month PFS, 57.2%; 95% CI, 39%-83%; $P < .0001$; Figure 6). Median OS was also significantly prolonged in patients who achieved a CR (24-month OS, 78%; 95% CI, 63%-97%; $P < .0001$). In a multivariate analysis, lower serum levels of lactate dehydrogenase prior to lymphodepletion were associated with an increased probability of a CR (odds ratio, 0.51; 95% CI, 0.26-0.90; $P = .03$). A higher peak level of CD8-positive CAR T cells was also associated with an improved PFS, OS, and likelihood of CR. In patients with aggressive NHL, landmark multivariable analysis identified factors associated with a superior response. At baseline, a higher

TRIAL IN PROGRESS ZUMA-7: A Phase 3 Randomized Trial of Axicabtagene Ciloleucel Versus Standard-of-Care Therapy in Patients With Relapsed/Refractory DLBCL

The ongoing randomized phase 3 ZUMA-7 trial (A Study Evaluating the Efficacy of Axicabtagene Ciloleucel Compared to Standard of Care Therapy in Subjects With Relapsed/Refractory Diffuse Large B Cell Lymphoma) is comparing axicabtagene ciloleucel vs the standard of care as second-line treatment for patients with relapsed or refractory DLBCL (Abstract TPS7585). The planned enrollment is 350 patients. First-line therapy must include an anti-CD20 antibody and an anthracycline. Patients who achieve a response to axicabtagene ciloleucel must intend to proceed to autologous SCT. Exclusion criteria include active infection, prior CD19-directed therapy, and prior SCT. Bridging chemotherapy is allowed for patients with a high disease burden at screening. After leukapheresis, patients in the axicabtagene ciloleucel arm will receive 3 days of lymphodepletion chemotherapy, consisting of fludarabine plus cyclophosphamide, followed by a single infusion of axicabtagene ciloleucel at a dose of 2×10^6 CAR T cells/kg. Patients in the standard-of-care arm will receive second-line treatment consisting of rituximab plus a chemotherapy regimen selected by the investigator. Patients who demonstrate a response after 2 or 3 cycles will receive high-dose therapy and undergo autologous SCT. The trial's primary endpoint is EFS, and secondary endpoints include ORR, OS, PFS, duration of response, patient-reported outcomes, adverse events, and clinically significant changes in safety laboratory values. The trial is accruing patients.

peak level of IL-7 and a lower level of IL-18 were each associated with a 24-month PFS rate of 100% ($P=.002$) among patients with aggressive NHL who achieved a CR.

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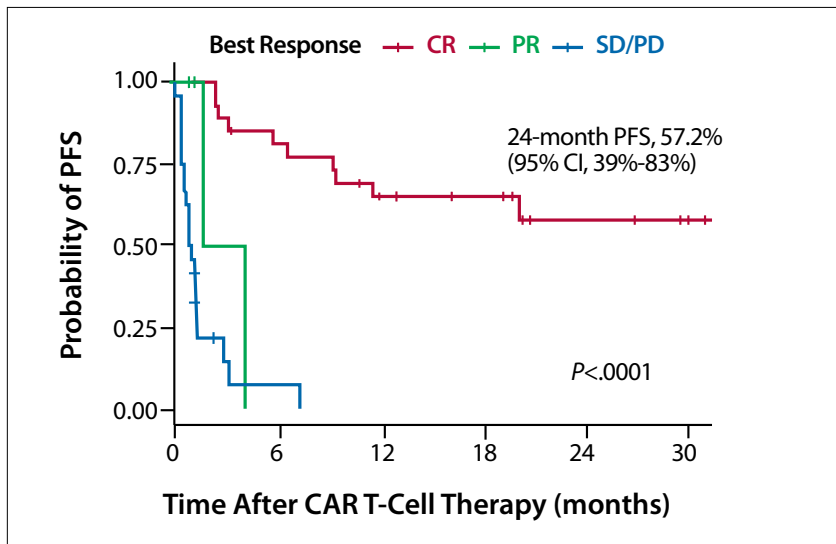


Figure 6. Progression-free survival in a study of factors that affect disease response and related outcomes in lymphoma patients treated with CAR T-cell therapy. CAR, chimeric antigen receptor; CR, complete response; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease. Adapted from Gauthier J et al. ASCO abstract 7567. *J Clin Oncol*. 2018;36(15 suppl).⁴

Randomized Phase 2 Trial of Polatuzumab Vedotin With Bendamustine and Rituximab in Relapsed/Refractory FL and DLBCL

Polatuzumab vedotin is an antibody-drug conjugate directed at CD79b, a marker that is universally expressed on follicular lymphoma and DLBCL cells. After binding, polatuzumab vedotin is internalized and the cytotoxic moiety, monomethyl auristatin E (MMAE), is released. In the safety run-in phase of a phase 1b/2 trial, polatuzumab vedotin combined with bendamustine and rituximab yielded promising response rates in heavily pretreated patients with follicular lymphoma and DLBCL.¹ Dr Laurie Sehn presented safety and efficacy findings from the phase 2 portion of the trial.² The trial randomly assigned 80 patients with follicular lymphoma and 80 with DLBCL in separate cohorts to receive 6 cycles of bendamustine plus rituximab, with or without polatuzumab vedotin.

TRIAL IN PROGRESS ZUMA-2: Phase 2 Multicenter Study Evaluating Efficacy of KTE-C19 in Patients With Relapsed/Refractory Mantle Cell Lymphoma

Patients with mantle cell lymphoma show high initial response rates to treatment. However, nearly all patients eventually progress, and response rates to salvage therapies are poor (Cheah CY et al. *J Clin Oncol*. 2016;34[11]:1256-1269). ZUMA-2 (Phase 2 Multicenter Study Evaluating Efficacy of KTE-C19 in Patients With Relapsed/Refractory Mantle Cell Lymphoma) is a multicenter, open-label, pivotal phase 2 trial evaluating axicabtagene ciloleucel (also known as KTE-19) in patients with relapsed or refractory mantle cell lymphoma (Abstract TPS3102). Eligible patients have received up to 5 prior therapies; prior treatment with chemotherapy, an anti-CD20 antibody, and a Bruton tyrosine kinase inhibitor is mandatory. The trial will exclude patients who underwent prior allogeneic SCT. After leukapheresis and 3 days of lymphodepleting chemotherapy with fludarabine and cyclophosphamide, 80 patients in 2 cohorts will receive a single infusion of axicabtagene ciloleucel at a dose of 2.0×10^6 CAR T cells/kg or 0.5×10^6 CAR T cells/kg. Bridging chemotherapy is allowed. The trial's primary objective is ORR, with secondary endpoints in safety and efficacy.

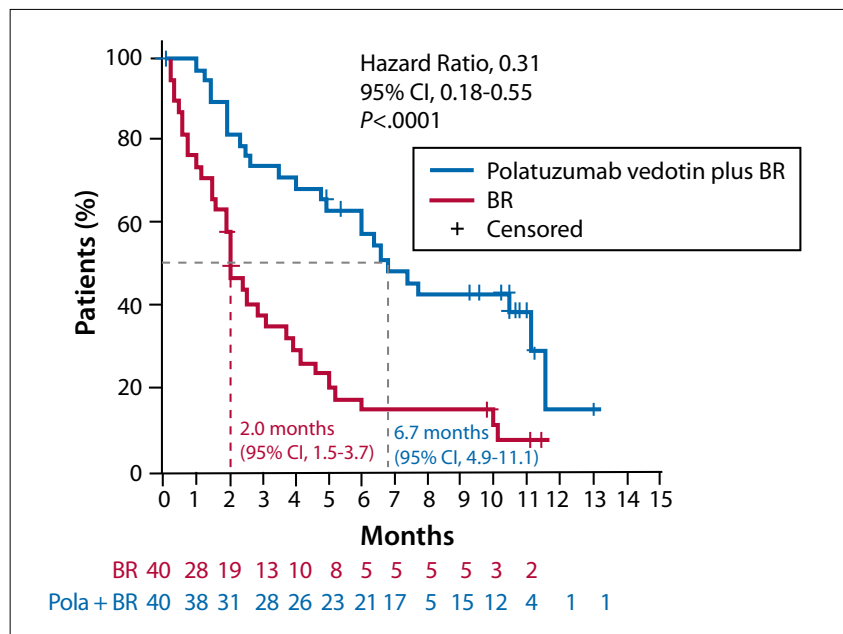


Figure 7. Progression-free survival among patients with DLBCL treated with bendamustine and rituximab with or without polatuzumab vedotin. DLBCL, diffuse large B-cell lymphoma; BR, bendamustine and rituximab; Pola, polatuzumab vedotin. Adapted from Sehn LH et al. ASCO abstract 7507. *J Clin Oncol.* 2018;36(15 suppl).²

ABSTRACT SUMMARY Treatment of Relapsed/Refractory B-Cell Malignancies by Chimeric Antigen Receptor T Cells Cultured From 50-100 mL Peripheral Blood in 7-10 Days

A study was conducted to reduce the time required for manufacturing CART cells (Abstract 7034). Between 50 mLs and 100 mLs of peripheral blood was extracted from 29 patients with relapsed or refractory B-cell malignancies. All patients received lymphodepletion chemotherapy with fludarabine and cyclophosphamide. After culture for 7 to 10 days, engineered T cells were administered in doses ranging from 1×10^6 cells/kg to 3×10^6 CART T cells/kg. CART T cells expanded by approximately 5×10^8 over 7 to 10 days, and the culture success rate was 100%. The ALL cohort included 13 adult and 4 pediatric patients. Sixteen ALL patients achieved a CR after CART T-cell therapy, and 1 patient died of cytokine release syndrome. The ORR was 71.4% at 3 months. Cytokine release syndrome occurred in 12 patients and was severe in 2 patients. Among 12 patients with B-cell lymphoma, the ORR was 75%, including 4 patients (33%) with a CR. At 6 months, the ORR was 50.0%, and the CR rate was 37.5%. Two patients developed cytokine release syndrome.

Treatment cycles were 28 days for the follicular lymphoma patients and 21 days for those with DLBCL. The primary endpoint was CR confirmed by ¹⁸F-fluorodeoxyglucose positron emission tomography (PET-CR), as

evaluated by an independent review committee (using modified Lugano criteria) at 6 to 8 weeks after the end of treatment.³ Patients who had undergone prior allogeneic SCT were excluded from the analysis.

The baseline characteristics were generally well-balanced between the 2 treatment arms for both sets of patients. However, in the follicular lymphoma cohort, more patients in the polatuzumab vedotin arm had a Follicular Lymphoma International Prognostic Index (FLIPI) score of 3 or higher (64% vs 37%). In the DLBCL cohort, more patients treated with bendamustine plus rituximab alone had an IPI of 3 or higher (73% vs 55%). Patients in all 4 arms had received a median of 2 prior lines of therapy.

Among patients with follicular lymphoma, the use of polatuzumab vedotin did not improve outcome. The PET-CR rates were 63% with bendamustine and rituximab alone vs 69% with the addition of polatuzumab vedotin. ORR was 73% vs 77%, respectively. The median PFS was 17.3 months vs 17.0 months ($P=.58$).

In contrast, in DLBCL patients, the polatuzumab vedotin combination yielded a significantly improved ORR (45% vs 18%; $P=.008$) and CR rate (40% vs 15%; $P=.012$). DLBCL patients in the polatuzumab combination arm also demonstrated a prolonged PFS (6.7 months vs 2.0 months; $P<.0001$; Figure 7) and OS (11.8 months vs 4.7 months; $P=.0008$). In a subgroup analysis, the polatuzumab vedotin combination was superior to bendamustine plus rituximab alone regardless of the patient’s number of prior lines of therapy or refractory status.

In the follicular lymphoma cohort, 74% to 76% of patients in each arm completed 6 cycles of treatment. In the DLBCL cohort, 23% treated with bendamustine plus rituximab alone and 49% of those treated with the polatuzumab vedotin combination completed all 6 treatment cycles. Among all patients, serious AEs were more common in those treated with polatuzumab vedotin plus bendamustine and rituximab (55% vs 33%). Serious AEs included infections (23% vs 18%) and febrile neutropenia (12%

vs 3%). The 2 treatment regimens yielded similar rates of grade 3 to 5 infections (16% vs 19%) and peripheral neuropathy (0% vs 1%).

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Radiotherapy to Bulky and Extralymphatic Disease in Combination With 6×R-CHOP-14 or R-CHOP-21 in Young Good-Prognosis DLBCL Patients: Results of the 2×2 Randomized UNFOLDER Trial of the DSHNHL/GLA

There is keen interest in defining the best use of radiation therapy in young patients with DLBCL.¹ The phase 3 UNFOLDER study (Rituximab and Combination Chemotherapy With or Without Radiation Therapy in Treating Patients With B-Cell Non-Hodgkin's Lymphoma) evaluated rituximab plus

cyclophosphamide, doxorubicin, prednisone, and vincristine (R-CHOP) with or without radiation therapy in young patients with DLBCL. The trial was conducted by the German High-Grade Non-Hodgkin's Lymphoma Study Group. R-CHOP therapy was administered in 14-day or 21-day cycles. Eligible patients were ages 18 to

60 years and qualified to receive radiotherapy to bulky or extralymphatic tumor sites. Patients were randomly assigned to treatment in a 2 × 2 factorial design, and the primary endpoint was event-free survival (EFS). The study included 467 patients in the 4 arms. Patients had a median age of 44 years (range, 18-60 years). Thirty-five percent of patients had stage III/IV disease, 52% had extralymphatic involvement, and 76% had bulky disease. The most common B-cell lymphoma subtype was DLBCL (89%). A planned interim analysis of the first 285 patients showed a significant improvement in EFS among patients who received radiotherapy ($P=.004$), and led to the protocol-defined closure of the 2 arms that did not include radiotherapy.

The final analysis of data from the UNFOLDER trial included 305 patients assigned to radiotherapy plus R-CHOP and 162 assigned to R-CHOP alone.² Protocol adherence and toxicity findings were similar for R-CHOP-14 and R-CHOP-21, as were EFS ($P=.591$), PFS ($P=.304$), and OS ($P=.575$). The CR/unconfirmed CR rate was 79% in patients who did not receive radiotherapy vs 90% in those who did. After a median of 66 months of observation, 3-year EFS was superior in patients who received

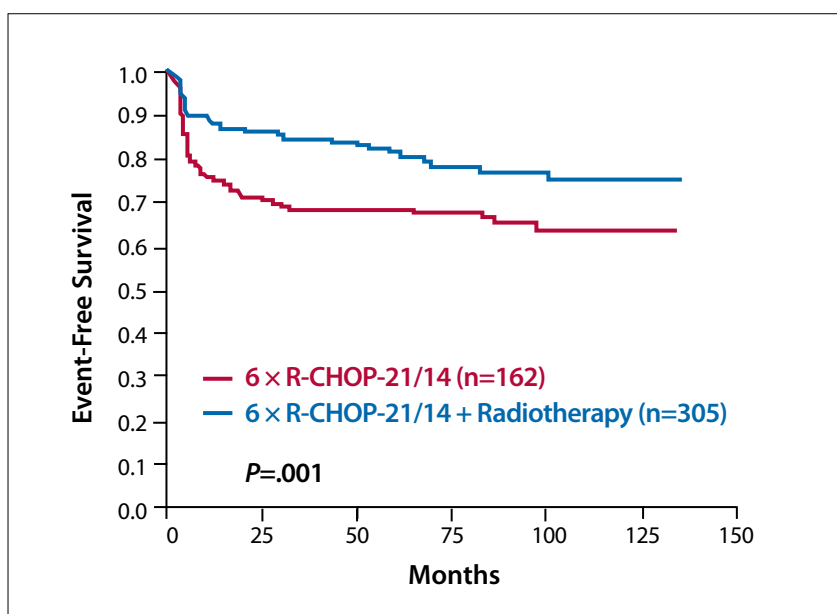


Figure 8. Event-free survival in the UNFOLDER trial. R-CHOP, rituximab plus cyclophosphamide, doxorubicin, prednisone, and vincristine; UNFOLDER, Rituximab and Combination Chemotherapy With or Without Radiation Therapy in Treating Patients With B-Cell Non-Hodgkin's Lymphoma. Adapted from Pfreundschuh M et al. ASCO abstract 7574. *J Clin Oncol*. 2018;36(15 suppl).²

radiotherapy (84% vs 68%; $P=.001$; Figure 8). The reduced EFS in patients who did not receive radiotherapy was linked to a higher rate of PRs (11% vs 2%) that triggered additional treatment that qualified as an EFS event. However, 3-year PFS was not significantly better among patients treated with radiotherapy vs those treated with R-CHOP alone (89% vs 81%;

$P=.221$). Three-year OS was 93% for patients treated with or without radiotherapy ($P=.506$). The findings were confirmed by multivariate analysis that adjusted for elevated lactate dehydrogenase levels, disease stage, and presence of bulky disease or extranodal involvement. Similar results were produced by restricting the analysis to patients with bulky disease only.

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Phase I/II Clinical Trial of Ibrutinib and Buparlisib in Relapsed/Refractory Diffuse Large B-Cell Lymphoma, Mantle Cell Lymphoma, and Follicular Lymphoma

Preclinical studies have shown synergistic activity between Bruton tyrosine kinase and inhibitors of phosphoinositide 3-kinase in models of B-cell NHL.^{1,2} A phase 1/2 clinical trial evaluated the efficacy and safety of ibrutinib plus buparlisib, a pan-phosphoinositide 3-kinase inhibitor, in patients with relapsed or refractory DLBCL, follicular lymphoma,

or mantle cell lymphoma.³ The trial used a standard 3 + 3 dose-escalation design with 4 dose levels. Ibrutinib and buparlisib were administered daily in 28-day cycles. The trial enrolled 14 patients with DLBCL, 5 with follicular lymphoma, and 18 with mantle cell lymphoma. Patients had a median age of 70 years (range, 48-84 years), and 73% were male. The median number

of prior lines of treatment was 3 for patients with DLBCL, 2 for those with follicular lymphoma, and 1 for those with mantle cell lymphoma.

Based on Lugano criteria, the ORR was 51%, including a CR rate of 43%. In the B-cell NHL subtypes, ORRs were 29% for DLBCL (CR of 21%), 20% for follicular lymphoma (CR of 20%), and 76% for mantle cell lymphoma (CR of 71%). The median time to response was 1.7 months (range, 1.6-2.0 months) in mantle cell lymphoma patients and 2.1 months in those with DLBCL (range, 1.6-11.8 months). The best percent change in SPD is shown in Figure 9. Targeted next-generation sequencing of circulating cell-free DNA is being conducted to explore tumor evolution. Targeted sequencing showed a decrease in mutation number and variant allele frequency in a patient who achieved an initial PR that subsequently converted to a CR.

The most common AEs of any grade were hyperglycemia, bilirubin elevation, diarrhea, and thrombocytopenia. Treatment-related AEs of grade 3 or higher were observed in 61% of patients; the most common of these events were rash (22%), hyperglycemia

ABSTRACT SUMMARY Lenalidomide With R-IMED (Rituximab, Ifosfamide, Methotrexate, Etoposide and Dexamethasone) in Refractory or Relapsed Non-GCB Diffuse Large B-Cell Lymphoma: A Phase II Clinical Trial

A phase 2 study investigated the combination of lenalidomide plus rituximab, ifosfamide, methotrexate, etoposide, and dexamethasone (R-IMED) in patients with previously treated non-germinal center B-cell subtype DLBCL (Abstract 7553). Eligible patients were adults with relapsed or refractory disease after R-CHOP. In addition to lenalidomide (10 mg daily, days 1-14), patients received 4 to 6 cycles of R-IMED every 21 days. The 40 patients had a median age of 51 years (range, 20-85 years), and 60% were male. Half had relapsed disease. The ORR was 70% and included a CR rate of 55%. After a median follow-up of 14.8 months, the median PFS was 10.9 months (95% CI, 7.9-13.9 months). The median PFS of patients who achieved a CR was 28.6 months (95% CI, 8.6-48.5 months). The median OS was not reached. No treatment discontinuations occurred owing to hematologic toxicity. The most common hematologic AE was neutropenia, and the most common nonhematologic AE was fatigue. Grade 3/4 nonhematologic events were rare, and no treatment-related deaths occurred.

Dose-Adjusted-EPOCH-R With High-Dose Methotrexate for Newly Diagnosed Stage II-IV CD5-Positive Diffuse Large B-Cell Lymphoma: Primary Analysis of the PEARL5 Study

In the 5% to 10% of DLBCL cases that express CD5, the disease is characterized by an aggressive course, with relapse commonly observed in the central nervous system.¹ A retrospective study showed that adding rituximab to CHOP improved OS ($P=.002$) and yielded a 2-year PFS of 51%. However, this strategy did not reduce the incidence of central nervous system relapse ($P=.89$) in patients with newly diagnosed DLBCL.² The single-arm, multicenter, phase 2 PEARL 5 study investigated dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin plus

rituximab (DA-EPOCH-R) followed by high-dose methotrexate in patients with newly diagnosed DLBCL.³ Treatment was administered in 4 cycles of DA-EPOCH-R, followed by 2 cycles of high-dose methotrexate, followed by 4 more cycles of DA-EPOCH-R. Eligible patients had stage II to IV disease, were ages 20 to 75 years, and had an ECOG performance status of 0 to 3. The primary endpoint was 2-year PFS. An interim analysis showed a CR rate of 91%, with manageable toxicity.

Dr Kana Miyazaki presented results of the primary analysis of the PEARL 5 study.⁴ The 47 patients had

a median age of 62 years, and 60% were older than 60 years. Fifty-three percent had stage III/IV disease, 34% had more than 1 extranodal disease site, and 85% had activated B-cell DLBCL. After a median follow-up of 3.1 years, primary endpoint analysis revealed a 2-year PFS of 79% (95% CI, 64%-88%; Figure 10), which compared favorably with the historical control of 51% seen with R-CHOP. Two-year OS was 89% (95% CI, 76%-95%), and the 2-year rate of central nervous system relapse was 9% (95% CI, 3%-21%). Three of these patients experienced central nervous system relapse prior to administration of high-dose methotrexate, including 2 patients with high-grade B-cell lymphoma with *MYC* rearrangement and 1 patient who discontinued treatment after the first rituximab cycle owing to grade 4 tumor lysis syndrome. In patients with activated B-cell DLBCL, the 2-year PFS was 77% and 2-year OS was 87%. Possible secondary malignancies were documented in 3 patients.

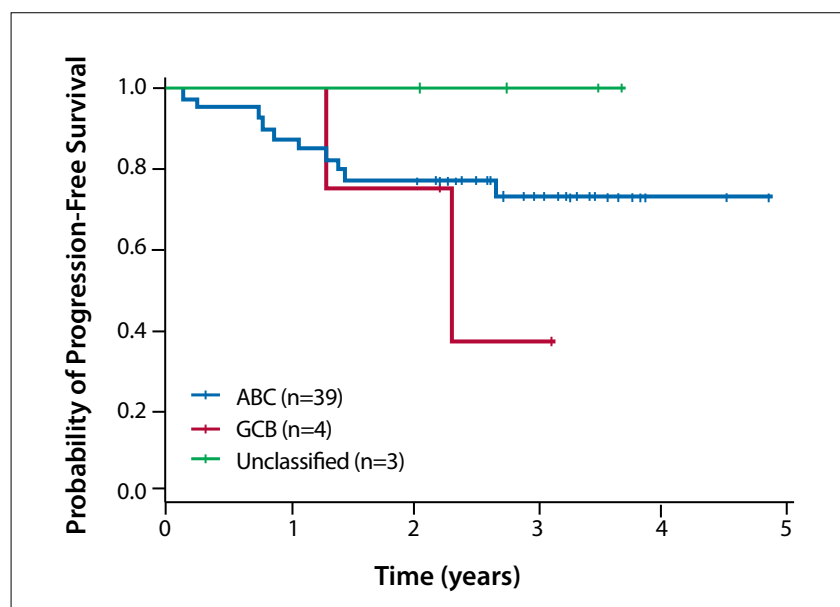


Figure 10. Probability of progression-free survival in a trial of DA-EPOCH-R followed by high-dose methotrexate in patients with newly diagnosed DLBCL. ABC, activated B-cell; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell; DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin plus rituximab. Adapted from Miyazaki K et al. ASCO abstract 7561. *J Clin Oncol.* 2018;36(15 suppl).⁴

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Advances in Aggressive Lymphoma From the 2018 American Society of Clinical Oncology Annual Meeting: Commentary

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Several presentations at the 2018 American Society of Clinical Oncology annual meeting focused on the management of patients with aggressive lymphoma, such as diffuse large B-cell lymphoma (DLBCL). Studies provided updated data on the use of the chimeric antigen receptor (CAR) T-cell therapies, such as axicabtagene ciloleucel. New data were also presented on the use of radiotherapy after rituximab plus cyclophosphamide, doxorubicin, prednisone, and vincristine (R-CHOP) and for the novel therapies lisocabtagene maraleucel and polatuzumab vedotin.

CAR T-Cell Therapy

CD19 CAR T-cell therapy is now approved by the US Food and Drug Administration (FDA) for relapsed/refractory DLBCL and histological variants. Two products are approved: axicabtagene ciloleucel, which is co-stimulated by CD28, and tisa-genlecleucel, which is costimulated by 4-1BB. Before the advent of CAR T-cell therapy, this patient population had an extremely poor overall survival.

Dr Frederick Locke presented an analysis of the durability response in ZUMA-1 (A Phase 1-2 Multi-Center Study Evaluating KTE-C19 in Subjects With Refractory Aggressive Non-Hodgkin Lymphoma), the pivotal phase 2 study of the CAR T-cell therapy

axicabtagene ciloleucel in patients with refractory large B-cell lymphoma.^{1,2} The ZUMA-1 trial met its primary endpoint—the rate of objective response—at the interim and primary analyses.² The objective response rate was 82%, with a complete response rate of 54%. At a median follow-up of 15.4 months, these rates were 42% vs 40%, respectively. At 18 months, the overall rate of survival was 52%. These data led the FDA to approve axicabtagene ciloleucel in patients with non-Hodgkin lymphoma whose disease progressed despite 2 or more lines of therapy. The ZUMA-1 study provided data for 108 patients. Patients who achieved a complete response had an extremely good chance of remaining in response beyond 1 year.² At a median follow-up of 15.4 months, the median duration of response for patients achieving a complete response was not reached. Patients who at best achieved a partial response following axicabtagene ciloleucel had a median duration of response of only 1.9 months. This finding, however, ignores the fact that many patients who achieved a complete response had initially achieved a partial response.

More than half of the progressive events in the ZUMA-1 study occurred by month 3. The study authors aimed to define the treatment practice for patients at 3 months, which appeared

to be the clinically relevant time point to understand outcomes. They performed a time-to-response analysis for patients with an objective response or a complete response. They looked at the partial response and complete response rates at month 3 as prognostic factors for progression-free survival (PFS). The analysis found that 41% of patients who achieved a partial response eventually converted to a complete response. Most of those conversions occurred by the 3-month time point. However, some of them occurred as late as 1 year after therapy. Many patients had a partial response by 1 month, and their response could deepen over time. An analysis of PFS landmarked at 3 months after the administration of therapy showed that among patients with a complete response, the median PFS was not reached. Similarly, among patients with a partial response at 3 months, median PFS had not been reached after a median follow-up of 15.4 months. Perhaps most interesting, the study showed that the rates of 12-month PFS were almost identical in patients with a partial response or a complete response (78% vs 79%).

In conclusion, this analysis showed that patients can achieve a complete response as late as 1 year after infusion of axicabtagene ciloleucel. Patients with a partial or complete response at month 3 had a nearly 80%

likelihood of maintaining a response at month 12. Perhaps most importantly, these data suggest that among patients who received a single CAR T-cell therapy infusion and achieved a response by 3 months, consolidative therapy is not needed to maintain that response. In fact, response at 3 months may be prognostic for long-term remission.

Another analysis of data from ZUMA-1 evaluated response to axicabtagene ciloleucel according to the number of prior lines of therapy at the time of enrollment.³ Safety and efficacy outcomes were assessed according to the number of lines of prior therapy: 1 to 2; 3; 4; or 5 or more. (Salvage chemotherapy and autologous transplant were considered a single line of therapy.) The analysis identified no differences according to previous lines of therapy in terms of the product characteristics, such as the CD4-to-CD8 ratio, the number of naive and central memory T cells, and the transduction rate. There were some differences in baseline patient characteristics. For example, patients with 5 or more prior lines of therapy had a higher disease stage and a higher International Prognostic Index (IPI) score at the time of enrollment, as would be expected because their disease was more refractory. There were differences in the response rates to axicabtagene ciloleucel according to the number of prior lines of therapy. The objective response rate decreased in patients with more lines of therapy. Among patients with 1 to 2 prior lines of therapy, the response rate was 91%, vs 38% among patients with 5 or more. The rates of ongoing response at 1 year were 47% vs 23%, respectively.

The analysis further evaluated the impact of disease burden on response to therapy. Patients with more prior lines of therapy had increased disease burden as evaluated by the sum of the product of the diameters of their reference lesions on computed tomography (CT) scans. Patients with the highest

disease burden had the lowest chance for an ongoing response at 1 year. The objective responses were otherwise similar. Those patients with more disease burden tended to have more severe adverse events, particularly neurologic toxicity, and they had a greater need for tocilizumab or corticosteroids. This finding suggests that the more disease burden a patient has, the less effective axicabtagene ciloleucel will be. The ZUMA-1 trial did not allow for bridging therapy after collection of CAR T cells, so patients whose disease continued to grow may have had a decreased likelihood of responding to therapy or achieving a durable response.² Also important to note is that these data suggest that earlier referral for CAR T-cell therapy is preferable.

Dr Vinodh Pillai presented a study on the correlation between pre-CAR CD19 expression with responses and relapses after CAR T-cell therapy.⁴ The findings were similar to those seen in the ZUMA-1 trial.³ Increased tumor burden was predictive for poor expansion of the CAR T-cell product in vivo and for lower rates of response and durable response. These data again suggest that early referral and bridging chemotherapy could improve response rates in patients with DLBCL.

Dr Jordan Gauthier presented results from a study evaluating the duration of response after CD19-specific CAR T-cell therapy among patients with relapsed/refractory B-cell non-Hodgkin lymphoma.⁵ CAR T-cell therapy leads to durable remissions in approximately 40% of patients.² It is important to understand the factors that affect response in this nascent field. The study by Dr Gauthier used a 4-1BB costimulated CD19 CAR T-cell product that is administered in a defined 1-to-1 ratio of CD4-positive and CD8-positive CAR T cells. The study found similar results to those reported with other CD19 CAR T-cell products. CAR T-cell expansion, as measured by a higher peak CAR T-cell level in the patient and a

larger cumulative area under the curve, correlated with improved outcome. It appears that some of the clinical factors that affect response to chemotherapy also impact response to CAR T cells. Poorer outcome was associated with high tumor burden and a high score on the IPI, which consists of age, performance status, lactate dehydrogenase, extranodal disease, and stage. Tumor characteristics, such as indolent histology, and product characteristics, such as the proportion of CD8-positive CAR T cells, also impacted outcome. Based on these results, the next step will be to determine whether interventions such as tumor debulking or CAR T-cell product modification can improve the outcome of patients in the poor-risk group.

Radiotherapy After R-CHOP

Dr Michael Pfreundschuh described results from the 2-by-2 randomized controlled UNFOLDER trial (Unfavorable Low-Risk Patients Treated With Densification of R-Chemo Regimens), a German trial that evaluated radiotherapy to bulky and extranodal disease in combination with 6 cycles of R-CHOP-14 or R-CHOP-21 in young DLBCL patients with a good prognosis.⁶ Patients with DLBCL are often cured by upfront R-CHOP therapy. However, patients with bulky and extranodal disease may require consolidated radiotherapy at the end of R-CHOP therapy. The results of the UNFOLDER trial were highly anticipated, as this study aimed to determine if radiotherapy improves the outcome of young, good-risk patients with bulky or extranodal disease. This 4-arm, randomized controlled trial had a 2-by-2 design. It enrolled patients younger than 60 years with IPI scores of 0 to 1. In the first randomization, patients received R-CHOP every 2 weeks (R-CHOP-14) or every 3 weeks (R-CHOP-21) for 6 cycles. The results of this part of the trial were previously presented.⁷ There was no difference in

outcome whether R-CHOP was given every 2 weeks or 3 weeks.

The presentation by Dr Pfreundschuh provided data for the second randomization.⁶ One cohort received treatment with radiotherapy, 39.6 gray, delivered to bulky and extranodal sites. The other cohort received no radiotherapy, just observation. At the planned interim analysis of 285 patients, the primary endpoint, event-free survival, was superior in patients assigned to radiation therapy. The nonradiotherapy arms were therefore closed. However, one of the events that met the primary outcome of event-free survival was whether patients received additional therapy. As expected, the partial response rate (by CT imaging) was higher in the nonradiotherapy arm than the radiotherapy arm (11% vs 2%). This finding led the trial investigators to more frequently prescribe radiotherapy to patients in the nonradiotherapy arm, which then counted as an event. For this reason, more events were reported in the nonradiotherapy arm.

The secondary outcome of 3-year PFS was statistically similar, at 89% with radiotherapy vs 81% without ($P=.221$). The 3-year overall response for both treatment groups was 93%. This study may be underpowered to evaluate the PFS trend. In addition, the follow-up of 66 months may not be long enough to exhibit any negative consequences of radiotherapy on overall survival. This trial therefore does not answer the question of whether end-of-treatment radiotherapy should be administered to patients with bulky or extranodal disease, patients in partial remission, or any patients at all. In this trial, patients in the observation group who had a partial response at the end of treatment crossed over to the radiotherapy group. Another aspect to consider is that the study used CT scans, and not positron emission tomography (PET)/CT scans, to evaluate the end-of-treatment response. PET may be a better tool to stratify patients for further therapy. Indeed, the OPTIMAL

>60 study (Improvement of Therapy of Elderly Patients With CD20+ DLBCL Using Rituximab Optimized and Liposomal Vincristine) in elderly patients with DLBCL, conducted by the same group, suggested that radiotherapy can be avoided in end-of-treatment PET-negative patients according to a nonrandomized comparison.⁸

Novel Therapies

Dr Jeremy Abramson presented an updated analysis of safety and long-term clinical outcomes in the pivotal TRANSCEND NHL 001 trial (Study Evaluating the Safety and Pharmacokinetics of JCAR017 in B-Cell Non-Hodgkin Lymphoma), which evaluated lisocabtagene maraleucel (also known as JCAR017) in relapsed/refractory aggressive lymphoma.^{9,10} This trial consisted of a dose-finding cohort followed by a dose-expansion cohort. All of the patients with DLBCL received lymphodepleting chemotherapy consisting of fludarabine and cyclophosphamide, and 134 underwent leukapheresis. Lisocabtagene maraleucel was administered to 114 patients, but only 102 received a product with the conforming 1-to-1 ratio of CD4-to-CD8. Among these 102 patients, some received multiple infusions to achieve the appropriate dose, whereas others received a single infusion.

The study provided analysis for the full cohort of 102 patients, which consisted of patients in the dose-finding and dose-escalation cohorts, as well as for a core subset of 72 patients, defined as those with DLBCL who met the criteria for the pivotal dose cohort. Nearly all patients developed some treatment-emergent adverse events. Approximately 65% had CAR T-cell related adverse events, the most common of which were neutropenia and other cytopenias. Cytokine release syndrome was seen in approximately 37% of patients, and reported neurologic toxicities were low. In the full cohort, any-grade cytokine release syndrome was seen in 37% of patients,

but only 1% developed grade 3 to 4. Any-grade neurotoxicity occurred in 23% of patients, and grade 3 to 4 was reported in 13%.

There were high response rates among patients with DLBCL. The objective response rate was 75% in the full cohort and 80% in the core cohort. The 6-month complete response rate was 34% vs 41%, respectively, suggesting that the durability of lisocabtagene maraleucel is similar to that of other CAR T-cell products approved by the FDA for large-cell lymphoma.

Data were presented for a cohort analysis of patients with poor-risk DLBCL. Importantly, the 6-month objective response rate exceeded 60% in patients with double or triple hits and was approximately 45% in chemorefractory patients. Again, these rates are similar to those seen with other CAR T-cell products approved for large-cell lymphoma. The durability of responses was encouraging. Among patients with a complete response, the median duration of response was not reached.

Lisocabtagene maraleucel had a manageable safety profile at the dose levels evaluated. It is important to note that this trial allowed for bridging chemotherapy, which likely reduced tumor burden before infusion of CAR T cells and may have affected the toxicity rates.

A randomized phase 1b/2 trial evaluated the addition of polatuzumab vedotin to bendamustine and rituximab in patients with relapsed/refractory follicular lymphoma or DLBCL who were ineligible for transplant.¹¹ Polatuzumab vedotin is an antibody drug conjugate that targets CD79b. Antibody-drug conjugates bind to the targets on tumor cells and then are endocytosed into the cell. There, the drug conjugate—in this case, a strong antimetabolic drug known as monomethyl auristatin E (MMAE)—is cleaved off the antibody and exerts activity within the cell. This activity is reminiscent of a commonly used drug,

brentuximab vedotin, which targets CD30 and is approved for Hodgkin lymphoma and other lymphoid malignancies.¹² Polatuzumab vedotin targets CD79b, a transmembrane protein that is associated with the B-cell receptor universally expressed in DLBCL and follicular lymphoma. This protein transduces signaling downstream of the B-cell receptor, and many lymphomas are characterized by tonic or chronic active signaling through CD79b.¹³⁻¹⁵ In fact, mutations for CD79b are found in some patients with lymphoma, and CD79b may be a driver mutation in some cancers. Therefore, CD79b is an exciting target for antibody-drug conjugate therapy.

The trial enrolled 80 patients with follicular lymphoma and 80 with DLBCL. In each group, patients were randomly assigned to treatment with polatuzumab vedotin plus bendamustine and rituximab or bendamustine and rituximab alone. Dr Laurie Sehn presented efficacy and toxicity data based on an intention-to-treat analysis after 15 months of follow-up.¹¹ The complete response rate was measured by PET/CT. Among patients with DLBCL, the PET complete response rate was 40% with polatuzumab vedotin plus bendamustine and rituximab vs 15% with bendamustine and rituximab alone. The median PFS was 6.7 months vs 2.0 months, respectively, and the median overall survival was 11.8 months vs 4.7 months. Among patients with follicular lymphoma, there was no significant difference in the rates of complete response or PFS between the treatment groups.

There was increased toxicity in the polatuzumab vedotin group. The

peripheral neuropathies that occurred were generally low-grade and reversible; only 1 patient developed grade 3 peripheral neuropathy. There was an increased rate of grade 3 to 5 cytopenias and febrile neutropenia, but infectious rates were not higher. Overall, polatuzumab vedotin appeared to be tolerable.

The findings in DLBCL are important because patients with relapsed/refractory disease have a poor outcome. The most effective treatment in this patient population, CD19 CAR T-cell therapy, may not be feasible or available for all patients. It is exciting to have a new drug that is active in DLBCL. Future trials will define the optimal combination regimen for polatuzumab vedotin and determine whether it can be a successful component of frontline therapy in previously untreated patients.

Disclosures

Dr Locke has served as a scientific advisor to Kite Pharma and as a consultant to Cellular Biomedicine Group Inc. Dr Jain has no real or apparent conflicts of interest to report.

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