

Subject: Chimeric Antigen Receptor T-cell Therapy (CAR T-cell): Yescarta (axicabtagene ciloleucel)		Original Effective Date: 4/12/18
Molina Clinical Policy (MCP) Number: MCP-396 (formerly 317b)	Revision Date(s): 3/11/2019; 4/23/20	
Review Date: 3/11/19; 4/23/20; 2/8/21		
MCPC Approval Date: 3/11/2019; 4/23/20; 2/8/21		

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DISCLAIMER

This Molina clinical policy is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina clinical policy document and provide the directive for all Medicare members.

RECOMMENDATION

This policy addresses Yescarta (axicabtagene ciloleucel) for the labeled indications of diffuse large B-cell lymphoma (DLBCL).

Molina Healthcare reserves the right to update this Policy and revise coverage criteria to include or omit any off-label condition(s) as necessary based on medical literature and clinical studies that may become available.

Chimeric antigen receptor T-cell therapy (CAR T-cell therapy), a type of immunotherapy which may also be referred to as adoptive T cell therapy, attempts to program individuals' own immune systems to recognize and attack cancer cells. CAR T-cells and genetically engineered TCR T-cells are manufactured by collecting lymphocytes from a patient or donor and modifying them *ex vivo* through gene transfer techniques. Viral vectors are introduced that express cell receptors that are highly specific for tumor antigens. CAR T and TCR T-cells are then infused back into a patient's body, where they direct a targeted immune response to cancerous tissue. CAR T cells, which are the focus of this report, express a hybrid receptor with an extracellular single-chain antibody fragment, a transmembrane domain, and at least 1 intracellular signaling domain. CAR T-cells are most often used to treat hematological malignancies, and a common target is B-cell cluster of differentiation antigen 19 (CD19). CAR T-cell infusion is typically administered in an outpatient setting, although patients receiving treatment may require an inpatient stay if adverse events are encountered. Patients typically must remain close to the treatment facility or clinic for a period of up to 6-8 weeks for monitoring and rapid identification of treatment-related adverse events that require hospitalization. CAR T therapy is associated with serious complications, including some fatal neurologic events and cytokine release syndrome (CRS), which is a severe systemic response (e.g., high fever, flu-like symptoms, hypotension, mental status changes) to the activation and proliferation of CAR T-cells. CRS is observed in nearly all treated patients and may be life-threatening, but it typically responds to treatment with aggressive supportive care that includes tocilizumab and corticosteroids. Neurologic toxicities may also be severe or life-threatening. Other adverse events include hypersensitivity reactions, serious infections, prolonged cytopenias, prolonged hypogammaglobulinemia, and second malignancies.

Yescarta (axicabtagene ciloleucel)

Axicabtagene is CD19-directed genetically modified autologous T cell immunotherapy. Axicabtagene ciloleucel is a type of chimeric antigen receptor therapy (CAR T). Axicabtagene ciloleucel reprograms an individual's own T cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19 expressing malignant and normal B cells. Treatment involves removing, genetically modifying, and then re-infusing an individual's own T-cells.

Safety and Efficacy of KTE-C19 in Adults with Refractory Aggressive Non-Hodgkin Lymphoma (ZUMA-1)

Efficacy of axicabtagene was studied in a single-arm, open-label, multicenter trial evaluated the efficacy of a single infusion of axicabtagene in adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma (ZUMA-1). Eligible patients had refractory disease to the most recent therapy or relapse within 1 year after autologous hematopoietic stem cell transplantation (HSCT). The study excluded patients with prior allogeneic HSCT, any history of central nervous system lymphoma, ECOG performance status of 2 or greater, absolute lymphocyte count less than 100/ μ L, creatinine clearance less than 60 mL/min, hepatic transaminases more than 2.5 times the upper limit of normal, cardiac ejection fraction less than 50%, or active serious infection. [ZUMA-1]. In total, 101 of 111 patients who underwent leukapheresis received Yescarta and most (76%) had DLBCL, 16% of patients had transformed follicular lymphoma, and 8% of patients had primary mediastinal large B- cell lymphoma. The median number of prior therapies was three. The median dose was 2.0×10^6 CAR- positive viable T cells.

Efficacy was established based on complete remission (CR) rate and duration of response (DOR), as determined by an independent review committee. The median time to response was 0.9 months (range: 0.8 to 6.2 months). Response durations were longer in patients who achieved CR, as compared to patients with a best response of partial remission (PR) (Table 6). Of the 52 patients who achieved CR, 14 initially had stable disease (7 patients) or PR (7 patients), with a median time to improvement of 2.1 months (range: 1.6 to 5.3 months).

FOOD AND DRUG ADMINISTRATION (FDA)

Yescarta (axicabtagene ciloleucel) is the second CAR T-cell therapy approved by the U.S. Food and Drug Administration (FDA). Axicabtagene ciloleucel was granted breakthrough and priority review status by the FDA. The first CAR T-cell therapy approved was Kymriah (tisagenlecleucel) in August 2017.

Large B-cell lymphoma, relapsed or refractory Treatment of relapsed or refractory large B-cell lymphoma after 2 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.

Limitations of use: Not indicated for the treatment of patients with primary CNS lymphoma

Available as: Single-dose unit infusion bag: frozen suspension of genetically modified autologous T cells labeled for the specific recipient

Approved by the FDA: October 18, 2017

Boxed Warning

- Cytokine release syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving axicabtagene ciloleucel. Do not administer axicabtagene ciloleucel to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.
- Neurological toxicities, including fatal or life-threatening reactions, occurred in patients receiving axicabtagene ciloleucel, including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with axicabtagene ciloleucel. Provide supportive care and/or corticosteroids as needed.

Risk Evaluation and Mitigation Strategy (REMS)

Axicabtagene ciloleucel is available only through a restricted program under a REMS called the [Yescarta and Tecartus REMS Program](#)

CLASSIFICATION: Antineoplastic Agent, Anti-CD19; Antineoplastic Agent, CAR T Immunotherapy; CAR T-Cell Immunotherapy; Cellular Immunotherapy, Autologous; Chimeric Antigen Receptor T-Cell Immunotherapy

CENTERS FOR MEDICARE & MEDICAID SERVICES (CMS)

National Coverage Determination (NCD) Manual 110.24

(Rev. 10454, Issued: 11-13-20, Effective: 08-07-19, Implementation: 02-16-21)

On August 7th, 2019 CMS published an NCD regarding CAR-T therapy coverage in the Medicare program. According to this NCD, for services performed on or after August 7, 2019, CMS covers autologous (your own blood-forming stem cells are collected) treatment for cancer with T-cells expressing at least one chimeric antigen receptor (CAR) when administered at healthcare facilities enrolled in the FDA risk evaluation and mitigation strategies (REMS) and used for a medically accepted indication as defined at Social Security Act section 1861(t)(2) -i.e., is used for either an FDA-approved indication (according to the FDA-approved label for that product), or for other uses when the product has been FDA-approved and the use is supported in one or more CMS-approved compendia. Reference Publication 100-03, National Coverage Determination (NCD) **Manual Section 110.24** for complete coverage criteria.

NOTE: On 11/2020, a Change Request (CR) was issued to inform of coverage effective for claims with dates of service on or after August 7, 2019 [Link: [TN 10454 \(Medicare Claims Processing\)](#)]

COVERAGE CRITERIA FOR INITIAL AUTHORIZATION

Yescarta (axicabtagene ciloleucel) may be authorized as a one-time, single administration intravenous infusion when ALL the following criteria are met:

- Prescribed by, or in consultation with, an oncologist/hematologist at a certified treatment center
- Diagnosis of Large B-cell lymphoma and ONE of the following subtypes: [ONE]
 - Diffuse large B-cell lymphoma (DLBCL); OR
 - Primary mediastinal large B-cell lymphoma (PMBCL or PMBL), OR
 - High grade B-cell lymphoma (HGBL), with MYC and BCL2 and/or BCL6 translocations (also referred to as double-hit or triple-hit lymphomas), OR
 - DLBCL arising from follicular lymphoma [also referred to as: follicular lymphoma with histological transformation to DLBCL or transformed follicular lymphoma (TFL)]

NOTE: Yescarta will not be authorized for a diagnosis of primary central nervous system lymphoma

- Relapsed or refractory disease, defined as ONE or more of the following: [ONE]
 - Unable to achieve a complete remission (CR) following second line of systemic chemotherapy, OR
 - Disease is in second or greater relapse/recurrence, OR
 - Relapsed after autologous hematopoietic stem cell transplantation (HSCT), OR
 - Relapsed transplant ineligible disease

- Required Documentation: [ALL]
 - Clinical notes from member's medical records including: all relevant history and physical exams, disease staging, all prior therapies and cancer treatment history, anticipated treatment course applicable, labs and/or tests supporting the diagnosis (lab results must be dated within 14 days of request); AND
 - Current weight for review of prescribed dosage
- Age 18 years or older
- Women of child-bearing potential: [ALL]
 - Negative serum pregnancy test within the past 30 days AND
 - Prescriber attestation that member has been counseled on the use of effective contraception during treatment

Informational: Treatment with axicabtagene ciloleucel is not recommended during pregnancy. If placental transfer were to occur, fetal toxicity, including B-cell lymphocytopenia, may occur. Refer to the cyclophosphamide and fludarabine monographs for information related to use of effective contraception in patients using these medications for lymphodepleting chemotherapy. The duration of contraception needed following axicabtagene ciloleucel administration is not known.

- Member has received TWO or more unique lines of systemic chemotherapy for their disease (which may or may not include therapy supported by stem cell transplant) [AT LEAST TWO]
 - An anthracycline-containing chemotherapy regimen; and
 - The ZUMA-1 trial included only patients that received prior anti-CD20 antibody therapy and an anthracycline-containing regimen.*
 - AND
 - Anti-CD20 monoclonal antibody (e.g., rituximab) unless the tumor is CD20 negative or the member has an FDA-labeled contraindication to anti-CD20 therapy – medical record documentation of the member's prior lines of therapy for their lymphoma must be submitted
 - AND
 - For transformed follicular lymphoma: Prior chemotherapy for follicular lymphoma with chemotherapy refractory disease after transformation to DLBCL
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Documentation of ALL the following clinical findings: [ALL]
 - Absolute neutrophil count (ANC) $\geq 1000/\text{uL}$; and
 - Absolute lymphocyte count (ALC) $> 100/\text{uL}$; and
 - Platelet count $\geq 75,000/\text{uL}$

- Member has adequate bone marrow, cardiac, pulmonary, and organ function and deterioration is not expected within four (4) weeks after Yescarta (axicabtagene ciloleucel) intravenous infusion, as determined by the treating oncologist/hematologist

NOTE: Lab results must be submitted within 14 days of the authorization confirming that member has adequate organ and bone marrow function and meets criteria

- If member has a history of allogeneic stem cell transplant: Documentation that member has no signs of active graft versus host disease (GVHD)

- Absence of the following conditions: [ALL]

- Active central nervous system (CNS) lymphoma by imaging
- Fungal, bacterial, viral or any active infection(s) that is *uncontrolled, including *but not limited to* the following: TB, Active hepatitis B (HBsAG positive) or hepatitis C (anti-HCV positive), HIV
 - *Uncontrolled or requires IV antimicrobials (antibiotics, antifungals, antiprotozoals, antivirals)*
- History or presence of CNS disorder such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement
 - ◆ NCCN guidelines define CNS involvement (CNS leukemia CNS-3) as the following: a white blood cell (WBC) count of ≥ 5 leukocytes/ μ L in the cerebrospinal fluid (CSF) with the presence of lymphoblasts*
- Vaccination with live virus vaccines within the past 6 weeks (prior to the start of lymphodepleting chemotherapy)
- Prior treatment with Yescarta™ (axicabtagene ciloleucel), Kymriah™ (tisagenlecleucel); or are being considered for treatment with any other gene therapy
- Active inflammatory disorders
- Active graft versus host disease (GVHD)

- Member will not receive ANY of the following:

- A G-CSF agent within the first 3 weeks after Yescarta (axicabtagene ciloleucel) infusion or until CRS has resolved; AND
 - ◆ Myeloid growth factors, particularly GM-CSF, are not recommended during the first 3 weeks after CAR T cell infusion or until CRS has resolved. Levels of G-CSF and GM-CSF have been found to be elevated in patients with severe neurotoxicity and may be related to its development*
- Live virus vaccine for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during treatment and until immune recovery following treatment with Yescarta (axicabtagene ciloleucel)

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and monitoring.

1. Recommended Dosage [ALL]

- Dosage prescribed is within the FDA-approved labeling based on indication of Large B-cell lymphoma (relapsed or refractory) [ALL]
 - One treatment course consists of lymphodepleting chemotherapy [cyclophosphamide 500 mg/m² intravenously and fludarabine 30 mg/m² intravenously on the fifth, fourth, and third day before infusion of Yescarta
AND
 - Target dose is 2×10^6 CAR-positive viable T cells per kg body weight, with a maximum dosage of 2×10^8 CAR-positive viable T cells

2. Authorization Limit [ALL]

- Initial/Continuation of Treatment [ALL]
 - Initial Authorization: ONE (1) single dose of Yescarta per lifetime
 - Concurrent Authorizations: Authorizations for Yescarta will also receive approval of Actemra (tocilizumab) for up to 6 months with quantity limits appropriate for the patient consistent with weight-based dosing
 - If severe or life-threatening cytokine-release syndrome (CRS) is suspected, administer Actemra as either 12mg/kg IV over 1 hour for patients <30kg or 8mg/kg IV over 1 hour for patients ≥ 30 kg*
 - Continuation of Treatment Authorization: NOT recommended
 - Repeat treatment of Yescarta (axicabtagene ciloleucel) for any indication is considered investigational, as the safety and efficacy beyond one dose has not been studied and is also not indicated in the current FDA approval for Yescarta (axicabtagene ciloleucel). The evidence is insufficient to determine the effects on net health outcomes.*

3. Route of Administration [ALL]

- Yescarta (axicabtagene ciloleucel) is considered a provider-administered medication via IV use only and must be administered in an authorized treatment center: <https://www.yescarta.com/treatment-centers>
- The treating facility is certified and complies with the Yescarta REMS requirements, including: [ALL]
 - Availability of a minimum of two doses of tocilizumab for each patient, if needed for treatment of cytokine release syndrome (CRS) post-treatment
 - Member will be monitored for signs and symptoms of CRS for at least 4 weeks after treatment and counselled to seek immediate medical attention if signs or symptoms of CRS or a neurological event
 - Member is within proximity (2 hours) of the certified healthcare facility for at least 4 weeks post-treatment
 - Assurance that healthcare providers who prescribe, dispense or administer Yescarta are trained in the management of CRS and neurologic toxicities

REAUTHORIZATION /CONTINUATION OF THERAPY

The safety and efficacy of repeat treatment has not been studied and is currently not supported by any compendia nor indicated in the current FDA approved labeling. Requests for reauthorization or beyond one dose is considered not medically necessary and will not be authorized.

COVERAGE EXCLUSIONS

All other uses of **Yescarta (axicabtagene ciloleucel)** that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy are considered experimental/investigational or not a covered benefit of this policy, including but not limited to the following, due to insufficient evidence in the peer-reviewed medical literature to support safety, efficacy, and net health outcomes. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

- Members who have had prior treatment with any form of CAR T-cell therapy
 - ◆ *Repeat administration of Yescarta (axicabtagene ciloleucel) experimental and investigational since the safety and efficacy beyond one dose has not been studied and is not indicated in the current FDA approval for Yescarta. The evidence is insufficient to determine the effects on net health outcomes.*
- Pregnancy: 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. Therefore, Yescarta is not recommended for women who are pregnant.
- Pediatric patients: The safety and efficacy of Yescarta have been established in pediatric patients; therefore, Yescarta is excluded in the pediatric population.
- Geriatric patients: Clinical trials of Yescarta did not include sufficient numbers of patients aged 65 years and older to determine they respond differently or have different safety outcomes as compared to younger patients.

SUMMARY OF EVIDENCE

DLBCL is an aggressive type of non-Hodgkin lymphoma (NHL) that affects B cells, interfering with a patient's immune response and ability to fight infection (Lymphoma Research Foundation, 2020). It is the most common type of NHL in the United States and worldwide with more than 18,000 new cases diagnosed each year (Lymphoma Research Foundation, 2020)

Treatment for Relapsed or Refractory Disease

High-dose chemotherapy followed by stem cell transplantation can be used to treat patients with DLBCL whose disease is refractory or relapsed following initial chemotherapy. Most patients undergoing stem cell transplantation will have an autologous transplant (patient receives his or her own stem cells, collected prior to the procedure). Occasionally, a patient will undergo an allogeneic transplant (patient receives stem cells from a donor).

- **Refractory DLBCL** refers to disease that fails to respond adequately to treatment. Primary refractory DLBCL refers specifically to an inadequate response to initial treatment.
- **Relapsed DLBCL** refers to disease that recurs after achievement of a complete response (CR) to initial treatment.

Yescarta (axicabtagene ciloleucel)

The ZUMA-1 Phase I and II clinical trials formed the basis of the US Food and Drug Administration approval of Axicabtagene ciloleucel (axi-cel).

The best available published evidence on Yescarta for relapsed or refractory DLBCL is the phase II pivotal ZUMA-1 trial (Neelapu et al., 2017). Also published are outcomes in 7 patients who participated in the phase I segment of the ZUMA-1 trial (Locke et al., 2017). A report on outcomes in 7 patients with chemotherapy-refractory DLBCL treated with the same CAR T-cell therapy construct as Yescarta (but manufactured differently) is also published (Kochenderfer et al., 2015).

Phase I ZUMA-1 trial (Locke et al., 2017): In the multicenter ZUMA-1 phase 1 study, KTE-C19, an autologous CD3 ζ /CD28-based chimeric antigen receptor (CAR) T cell therapy, was evaluated in patients with refractory DLBCL. Patients received low-dose conditioning chemotherapy with concurrent cyclophosphamide (500 mg/m²) and fludarabine (30 mg/m²) for 3 days followed by KTE-C19 at a target dose of 2×10^6 CAR T cells/kg. The incidence of dose-limiting toxicity (DLT) was the primary endpoint. Seven patients were treated with KTE-C19 and one patient experienced a DLT of grade 4 cytokine release syndrome (CRS) and neurotoxicity. Grade ≥ 3 CRS and neurotoxicity were observed in 14% (n = 1/7) and 57% (n = 4/7) of patients, respectively. All other KTE-C19-related grade ≥ 3 events resolved within 1 month. The overall response rate was 71% (n = 5/7) and complete response (CR) rate was 57% (n = 4/7). Three patients have ongoing CR (all at 12+ months). CAR T cells demonstrated peak expansion within 2 weeks and continued to be detectable at 12+ months in patients with ongoing CR. This regimen of KTE-C19 was safe for further study in phase 2 and induced durable remissions in patients with refractory DLBCL.

ZUMA-1 Trial (Neelapu et al., 2017): ZUMA-1 is a single-arm, Phase 2, multicenter, registrational trial at 22 sites. Eligible patients were aged 18 years or older, and had histologically confirmed diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL), or transformation follicular lymphoma (TFL) according to the 2008 WHO Classification of Tumors of Hematopoietic and Lymphoid Tissue; refractory disease or relapsed after autologous stem-cell transplantation; an Eastern Cooperative Oncology Group performance status of 0 or 1; and had previously received an anti-CD20 monoclonal antibody containing-regimen and an anthracycline-containing chemotherapy.

- A total of 111 patients were enrolled in the study. Axicabtagene ciloleucel (axi-cel) was manufactured for 110 patients (99%) and administered to 101 patients (91%); 77 patients with DLBCL, 8 patients with PMBCL, and 16 patients with TFL.
- Participants received one dose of axicabtagene ciloleucel on day 0 at a target dose of 2×10^6 CAR T cells per kg of bodyweight after conditioning chemotherapy with intravenous fludarabine (30 mg/m² body-surface area) and cyclophosphamide (500 mg/m² body-surface area) on days -5, -4, and -3.

- Patients who had an initial response and then had disease progression at least 3 months after the first dose of Yescarta could be retreated. The median turnaround time for production of Yescarta was 17 days.
- Yescarta was not successfully manufactured for 1 of the 10 patients not treated; other reasons for non-treatment included an adverse event prior to Yescarta infusion (n=4), death from disease progression (n=1), non-measurable disease (n=2), sepsis (n=1), and death from presumed tumor lysis syndrome (n=1). The median age of the study population was 58 years; 85% had stage III or IV disease, 21% had disease relapse within 12 months of ASCT, and 69% had a history of ≥ 3 prior lines of therapy.
- The primary endpoints were safety for phase 1 and the proportion of patients achieving an objective response for phase 2, and key secondary endpoints were overall survival, progression-free survival, and duration of response.
- The primary efficacy endpoint was objective response rate (partial and complete combined), as assessed when 92 patients could be evaluated 6 months after Yescarta infusion. This endpoint was compared with a preset historical objective response rate of 20%, which was based rates reported in the literature for refractory DLBCL. At a minimum of 6 months follow-up, the objective response rate was 82%, which was significantly superior to the historical objective response rate ($P < 0.001$). Among these patients, the overall complete response rate was 52%, with 47% of patients with DLBCL and 70% of patients with either PMBCL or TFL achieving a complete response. The median time to response was 1 month (range, 0.8 to 6.0) and the median duration of response was 8.1 months. CRS of any grade occurred in 95% of treated patients; grade 1 or 2 CRS was reported in 80% of patients, and 13% of patients had grade ≥ 3 CRS. Three patients died during treatment; 2 deaths were related to Yescarta.
- Included in this published report is an updated analysis of outcomes in 108 patients who participated in the phase I and II segments of the ZUMA-1 trial.
- At a minimum 1-year follow-up, the objective response rate remained 82%; the complete response rate was 58%. Progression-free survival rates (secondary endpoint) in this updated analysis were 44% at 12 months and 41% at 15 months. The median overall survival had not yet been reached. ClinicalTrials.gov, number NCT02348216

A total of 119 patients were enrolled and 108 received axicabtagene ciloleucel; 101 patients were evaluable at follow-up. Data were previously reported for a median follow-up of 15.4 months. The current study reported data at a median follow-up of 27.1 months, or about 2 years.

Long-term Safety and Efficacy Results of the ZUMA-1 trial

Two-year follow-up data from the ZUMA-1 trial of Yescarta (axicabtagene ciloleucel) in adult patients with relapsed for refractory large B-cell lymphoma were reported by Locke et al. (2019) which included 108 patients with refractory disease or relapse after ASCT who were followed for a median of 27 months.

- At a 2-year follow-up, 84 patients (83%) had an investigator-assessed objective response, 59 (58%) of which had a complete response. 39 patients (39%) had an investigator-assessed ongoing response, with a median duration of response of 11.1 months (range, 4.2 to not estimable). The median overall survival was not yet reached (range, 12.8 to not estimable). Patients had a median progression-free survival of 5.9 months (95% CI, 3.3-15.0). Grade 3-4 CRS occurred in 11% of patients, and grade 3-4 neurological events in 32%.

- Since the previous analysis at 1-year, additional serious adverse events were reported in 4 patients (grade 3 mental status changes, grade 4 myelodysplastic syndrome, grade 3 lung infection, and two episodes of grade 3 bacteremia), none of which were judged to be treatment related.
- 2 treatment-related deaths (due to hemophagocytic lymphohistiocytosis and cardiac arrest) were previously reported, but no new treatment-related deaths occurred during the additional follow-up.
- These 2-year follow-up data from ZUMA-1 suggest that Yescarta can induce durable responses and a median overall survival of greater than 2 years and has a manageable long-term safety profile in patients with relapsed or refractory large B-cell lymphoma and no additional treatment-related deaths or toxicity

Kochenderfer et al., 2015: The safety and efficacy of administering autologous anti-CD19 CAR T cells to patients with advanced CD19(+) B-cell malignancies was assessed in 15 patients with advanced B-cell malignancies. Nine patients had diffuse large B-cell lymphoma (DLBCL), two had indolent lymphomas, and four had chronic lymphocytic leukemia. Patients received a conditioning chemotherapy regimen of cyclophosphamide and fludarabine followed by a single infusion of anti-CD19 CAR T cells. The results showed that of 15 patients, eight achieved complete remissions (CRs), four achieved partial remissions, one had stable lymphoma, and two were not evaluable for response. CRs were obtained by four of seven evaluable patients with chemotherapy refractory DLBCL; three of these four CRs are ongoing, with durations ranging from 9 to 22 months. Acute toxicities including fever, hypotension, delirium, and other neurologic toxicities occurred in some patients after infusion of anti-CD19 CAR T cells; these toxicities resolved within 3 weeks after cell infusion. One patient died suddenly as a result of an unknown cause 16 days after cell infusion. CAR T cells were detected in the blood of patients at peak levels, ranging from nine to 777 CAR-positive T cells/ μ L. The report concluded that these results demonstrate the feasibility and effectiveness of treating chemotherapy-refractory B-cell malignancies with anti-CD19 CAR T cells. The numerous remissions obtained provide strong support for further development of this approach.

CAR T Therapy Systematic Reviews/Meta-Analyses

Holzinger et al., 2016: A meta-analysis evaluated CAR T cells targeted toward CD19 for B-cell malignancies. Fourteen clinical trials including 119 patients were included for analysis. The authors calculated an overall pooled response rate of 73% (95% CI, 46%-94%) and noted significant heterogeneity across studies ($P < 0.001$). Patients with ALL were found to have higher response rates than those with chronic lymphocytic leukemia or lymphoma (93% versus 62% and 36%). Some factors associated with improved responses included a lymphodepletion regimen and not using interleukin-2 to stimulate the cells (Zhang et al., 2015). In a 2016 comprehensive and notable narrative review, Holtzinger et al. (2016) list over 100 ongoing clinical trials evaluating CAR T cells with a variety of targets for a variety of indications. They note that the majority of trials are underway in the United States or Canada, and about a quarter of the trials are underway in China. They also briefly review 7 completed phase I trials on CAR T cells for hematological malignancy. The authors conclude that more research is needed to identify ideal CAR T cell targets, receptor designs, and lymphodepletion regimens; control toxic effects like CRS; and evaluate the use of CAR T cells with HSCT.

CAR T-cell therapy-associated TOXicity (CARTOX) Working Group

CARTOX published the guideline called Chimeric antigen receptor T-cell therapy assessment and management of toxicities (Neelapu et al., 2017). The guidelines summarize the two major toxicity's associated with CAR T therapy: 1) Cytokine-release syndrome (CRS), the most commonly observed toxicity, can range in severity from low-grade constitutional symptoms to a high-grade syndrome associated with life-threatening multiorgan dysfunction; rarely, severe CRS can evolve into fulminant haemophagocytic lymphohistiocytosis (HLH). 2) Neurotoxicity, referred to as CAR T-cell-related encephalopathy syndrome (CRES), is the second most-common adverse event, and can occur concurrently with or after CRS. The guidelines recommend that intensive monitoring and prompt management of toxicities is essential to minimize the morbidity and mortality associated with this potentially curative therapeutic approach that include a multidisciplinary approach to provide recommendations for monitoring, grading, and managing the acute toxicities that can occur in patients treated with CAR T-cell therapy.

The Foundation for the Accreditation of Cellular Therapy (FACT)

FACT is a U.S. based program that oversees the accreditation of centers that perform stem cell transplants and other types of cell-based therapies such as quality aspects of cellular therapy. The group published guidelines in 2018 'FACT Standards for Immune Effector Cells' which apply to cells used to modulate an immune response for therapeutic intent, including CAR T cells. These standards are designed to provide the requirements and minimum guidelines for programs, facilities, and individuals performing cell transplantation and therapy or providing support services for such procedures.

The Institute for Clinical and Economic Review (ICER)

ICER published a final Evidence Report (March 2018) entitled Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value. ICER's analyses reviewed outcomes for tisagenlecleucel in B-ALL and NHL and axicabtagene ciloleucel in NHL compared to outcomes in patients who received other therapies with similar FDA indications. Evidence is insufficient to judge whether one CAR T therapy is superior to the other for NHL. In general, the findings suggest that the CAR T therapies provide a net health benefit compared to standard chemoimmunotherapy regimens and found both therapies to be cost-effective in the long-term for the specified indications. However, at the current time there is uncertainty given that the studies of CAR T therapies are all single-arm trials that are small and have short follow-up. These uncertainties make the comparative efficacy analyses versus standard therapy controversial.

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)

B-Cell Lymphomas Version 4.2020

NCCN guidelines for B-cell lymphoma (V.4.2020) recommend Yescarta for the following:

- The treatment of a variety of B-cell lymphomas in individuals with relapsed or refractory disease and after at least two chemotherapy regimens.

Recommended indications include DLBCL which transformed from follicular lymphoma or nodal marginal zone lymphoma, DLBCL, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, AIDS-related B-cell lymphoma, human herpes virus 8 (HHV8)-positive DLBCL, and post-transplant lymphoproliferative disorders (category 2A) (NCCN, 2020b; NCCN, 2020c)

DEFINITIONS

Anti-CD20 monoclonal antibodies (mAbs): Used to achieve B cell depletion and were initially developed to treat B cell proliferative disorders, including non-Hodgkin's lymphoma and chronic lymphocytic leukemia.

Cytokine release syndrome (CRS):

- CRS is a systemic inflammatory response syndrome triggered in particular by the release of large amounts of interleukin-6. The release of cytokines induces fever, vascular leakage, and potentially direct myocardial injury. CRS is the most common toxicity associated with CAR T-cell therapy usually develops in the first or second week after CAR T-infusion.
- The severity of CRS symptoms can vary significantly, ranging from low grade with mild symptoms to high grade with early-onset high fevers, hyperpyrexia, high incidence of infections, and neurotoxicity. Moreover, severe CRS can be accompanied by excessive macrophage activation, coagulation dysfunction, tumor lysis syndrome, and involve any organ system in the body and lead to life-threatening multiorgan dysfunction including the cardiovascular, nervous, respiratory, gastrointestinal, hepatic, renal, and hematological systems
- In terms of management, mild to moderate CRS is usually self-limited and can be controlled with close observation, hydration, and supportive care. In contrast, severe CRS requires intensive medical management with tocilizumab alone or in combination with steroids.

ECOG (Eastern Cooperative Oncology Group)

Performance Status: A scale used to determine the individual's level of functioning; may also be referred to as the WHO (World Health Organization) or Zubrod score

- 0 Fully active, able to carry on all pre-disease performance without restriction
- 1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
- 2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3 Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
- 4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
- 5 Deceased

Refractory DLBCL refers to disease that fails to respond adequately to treatment. Primary refractory DLBCL refers specifically to an inadequate response to initial treatment.

Relapsed DLBCL refers to disease that recurs after achievement of a complete response (CR) to initial treatment.

APPENDIX

Additional warnings from the FDA PI Label (2020) include the following information and recommendations:

- *Serious hypersensitivity reactions*, including anaphylaxis, may occur due to the dimethyl sulfoxide (DMSO) or residual gentamicin in axicabtagene ciloleucel.

- *Serious infections* (including life-threatening infections) occurred in patients after axicabtagene ciloleucel infusion, including grades 3 and higher infections in close to one-quarter of patients. Viral and bacterial infections were reported as well as infections due to unknown pathogens. Begin prophylaxis according to local guidelines prior to axicabtagene ciloleucel infusion. Monitor for signs and symptoms of infection before and following treatment and manage appropriately; do not administer to patients with clinically significant active systemic infections. Neutropenic fever has been observed after axicabtagene ciloleucel infusion and may occur concurrently with CRS. If neutropenic fever occurs, evaluate for infection and manage with broad-spectrum antibiotics, fluids, and other supportive care as clinically indicated.
- *Prolonged cytopenias* may occur several weeks after lymphodepleting chemotherapy and axicabtagene ciloleucel infusion. Unresolved (by day 30 following axicabtagene ciloleucel treatment) grade 3 and 4 cytopenias included neutropenia, thrombocytopenia, and anemia. Monitor blood counts
- *Hypogammaglobulinemia and B-cell aplasia* may occur in patients receiving axicabtagene ciloleucel. Monitor immunoglobulin levels after axicabtagene ciloleucel treatment. Manage hypogammaglobulinemia with infection precautions, antibiotic prophylaxis, and immunoglobulin treatment (per standard replacement guidelines).
- *Secondary malignancy* Patients treated with axicabtagene ciloleucel may develop secondary malignancies or leukemia recurrence. Monitor permanently for secondary malignancies. If a secondary malignancy occurs, contact the manufacturer to obtain patient sampling instructions for testing.
- *Vaccination* with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during axicabtagene ciloleucel treatment, and until immune recovery following treatment. The safety of immunization with live viral vaccines during or following axicabtagene ciloleucel treatment has not been studied.

CODING INFORMATION: THE CODES LISTED IN THIS CLINICAL POLICY ARE FOR INFORMATIONAL PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE AND INCLUSION OR EXCLUSION OF ANY CODES DOES NOT GUARANTEE COVERAGE.

HCPCS	Description
Q2041	Axicabtagene ciloleucel, up to 200 million autologous anti-cd19 car positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose
0537T	Chimeric antigen receptor T-cell (CAR T) therapy; harvesting of blood-derived T lymphocytes for development of genetically modified autologous CAR T-cells, per day
0538T	Chimeric antigen receptor T-cell (CAR T) therapy; preparation of blood-derived T lymphocytes for transportation (e.g., cryopreservation, storage)
0539T	Chimeric antigen receptor T-cell (CAR T) therapy; receipt and preparation of CAR T cells for administration
0540T	Chimeric antigen receptor T-cell (CAR T) therapy; CAR T cell administration, autologous
ICD-10	Description
C82.00-C82.99	Follicular lymphoma
C83.30-C83.39	Diffuse large B-cell lymphoma
C85.20-C85.29	Mediastinal (thymic) large B-cell lymphoma
C91.00-C91.02	Acute lymphoblastic leukemia (ALL)

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- Available at: CMS NCD
- Decision Memo for Chimeric Antigen Receptor (CAR) T-cell Therapy for Cancers (CAG-00451N)
Available at: <https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=291>

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Policy History	Approval
<u>Policy Developed</u> AMR Peer Review: Policy was reviewed by practicing physician board certified in Internal Medicine, Oncology, Hematology, 11/21/2017	4/12/2018
<u>Policy Revision</u> AMR Peer Review: Policy was reviewed by practicing physician board certified in Oncology, 1/31/2019 <ul style="list-style-type: none"> • Previous policy (MCP-317) included both Kymriah and Yescarta; created individual policy for Kymriah (MCP-317a) and Yescarta (MCP-317b) • Notable revisions include: Revised coverage criteria in the Initial Recommendations; revisions in 'Exclusions' section; updated NCCN Clinical Practice Guidelines with summary from 'B-Cell Lymphomas Version 5.2018' 	3/11/2019
<u>Policy Revision</u> AMR Peer Review: Policy was reviewed by practicing physician board certified in Oncology, Hematology, 3/31/2020 Notable revisions include: <ul style="list-style-type: none"> • Added criterion for women of child-bearing potential requiring a negative pregnancy test 	4/23/2020

<ul style="list-style-type: none"> • Added ‘<i>Long-term Safety and Efficacy Results of the ZUMA-1 trial</i>’ in ‘Summary of Medical Evidence’ section • Added ‘<i>Lab results must be submitted within 14 days of the authorization</i>’ to criterion confirming that member has adequate organ and bone marrow function • Updated criteria in the ‘Recommendation’ section: ‘<i>Member does NOT meet or have any of the following conditions</i>’ to include ‘<i>Active central nervous system (CNS) lymphoma by imaging</i>’ and ‘<i>Vaccination with live virus vaccines within the past 6 weeks (prior to the start of lymphodepleting chemotherapy)</i>’ • Updated NCCN Clinical Practice Guidelines with summary from ‘B-Cell Lymphomas Version 2.2019’ 	
<p><u>Annual Review</u> The medical necessity criteria were not revised with this annual review. Content updates and revisions include:</p> <ul style="list-style-type: none"> • Updated NCCN guidelines on B-cell lymphoma (V.4.2020) recommendations for Yescarta • Insertion of a CMS Section outlining the NCD for implementation on 02-16-21 • Policy number updated to MCP-396 (from 317b) for clarity [Historical information: First policy developed was MCP-317 which included both Kymriah and Yescarta. Committee voted to split into individual policies for Kymriah (MCP-317a) and Yescarta (MCP-317b)] 	<p>MCPC 2/8/21</p>

**Annual Review and Policy Revisions: All content, clinical evidence, coverage criteria, practice guidelines, appendices and reference sections were reviewed and revised with the most recent medical literature and available evidence. Coverage criteria for Initial and Continuation of Therapy were revised/updated as appropriate.*