Overview

Large B-cell lymphoma (LBCL), a form of non-Hodgkin lymphoma (NHL), is characterized by an overproliferation of B cells of the immune system. NHL is a diverse group of distinct malignancies that originate from B cells or T cells. B-cell lymphomas account for approximately 85% of NHL cases in the United States. Patients diagnosed with a B-cell malignancy have a range of prognoses and treatment options that vary based on the stage of disease and whether it is considered relapsed or refractory (R/R). Signs and symptoms of NHL, such as diffuse large B-cell lymphoma (DLBCL), include enlarged lymph nodes; rapidly enlarging masses; fever, sweating, and chills; weight loss; fatigue; swollen abdomen; lack of appetite; chest pressure or pain; and shortness of breath. DLBCL is an aggressive form of NHL that affects B cells, interfering with a patient's immune response and ability to fight infection and is the most common type of NHL. Treatments options may include chemotherapy; immunotherapy; targeted therapy; radiation therapy; stem cell transplants; and, in rare cases, surgery. The current standard of care for the first-line treatment of DLBCL is chemotherapy with rituximab plus cyclophosphamide, hydroxydaunorubicin, vincristine and prednisolone (R-CHOP) [cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone] plus the monoclonal antibody rituximab (Rituxan) [Lymphoma Research Foundation; NCI]. The treatment strategy for a first relapse or primary refractory disease is guided by the eligibility of ASCT, which depends on multiple factors, including medical fitness, presence of comorbidities, performance status, and patient preference. CAR T-cell therapy targeting CD19 is a treatment option for patients who have poor-risk DLBCL with no other treatment options that seem viable. The FDA approved the use of Yescarta for the treatment of patients with R/R aggressive B-cell NHL based on the results from the ZUMA-1 clinical trial (Neelapu et al., 2017).

Follicular lymphoma (FL) is a type of B-cell lymphoma (BCL) and referred to as follicular since cancer cells tend to clump together in circles, known as follicles, in the lymph nodes. FL is a slow-growing or indolent form of NHL that arises from B-lymphocytes. Most FL cells have a specific chromosomal abnormality (a translocation between parts of chromosomes 14 and 18) that causes the overexpression of the gene BCL-2, which can cause the cells to become resistant to therapy (LLS, 2021). Patients with FL may have no obvious symptoms of the disease at diagnosis. Common symptoms of FL include enlargement of the lymph nodes in the neck, underarms, abdomen, or groin, as well as fatigue, shortness of breath, night sweats, and weight loss. Indolent NHL is a disease that starts out slowly but becomes more aggressive over time with each subsequent relapse. Treatment for indolent NHL ranges from observation with careful monitoring to aggressive therapy. Determining a treatment approach is based on multiple factors including prognostic factors, stage of disease, age and other medical conditions. FL is usually not considered to be curable, but more of a chronic disease. Currently, there are limited options for the treatment of R/R indolent FL after two or more lines of therapy. The accelerated FDA approval for R/R FL was supported by data from the primary analysis of the Phase 2 ZUMA-5 trial.

Yescarta (axicabtagene ciloleucel; axi-cel) is a gene-based immunotherapy, a form of CAR T-lymphocyte (T-cell) therapy, that involves adoptive cell transfer. It is an autologous CAR T-cell therapy that targets the CD19 protein on the surface of cancer cells referred to as a CD19-directed CAR T cell therapy. T cells are collected
from the patient and genetically modified using viral vectors to express CD19 cell receptors that are highly specific for B-lymphocyte (B-cell) antigens. The patient’s T-cells are collected and then modified in the lab, after which they are expanded and infused back into the individual to target the patient's own B-cell malignancy. Yescarta involves a single infusion of genetically modified T cells. The turnaround time from cell collection to reinfusion of the altered cells usually takes a few weeks. Low-dose chemotherapy is administered prior to the CAR-T infusion to deplete cancerous immune cells and make room for new immune cells. Yescarta is the first CAR T-cell therapy to receive FDA approval for large B-cell lymphoma and is also the first CAR T-cell therapy approved for patients with indolent follicular lymphoma.

**COVERAGE POLICY**

Yescarta (axi-cel) for the treatment of R/R large B-cell lymphoma (LBCL) and R/R follicular lymphoma (FL) may be considered medically necessary when **ALL** of the following clinical criteria are met (A AND B):

A. Member meets **ONE** of the following diagnosis of R/R LBCL or R/R FL (**1 OR 2**):

1. **Definitive diagnosis of R/R LBCL** documented by **ALL** of the following (a-c):
   a. Histologically confirmed diagnosis of **ONE** of the following:
      o Diffuse large B-cell lymphoma (DLBCL); **OR**
      o Primary mediastinal large B-cell lymphoma (PMBCL); **OR**
      o 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**
      o DLBCL arising from FL (also referred to as: FL with histological transformation to DLBCL); **OR**
      o Transformed Follicular Lymphoma (TFL) to DLBCL.
   
   **NOTE:** Yescarta will not be authorized for a diagnosis of primary CNS lymphoma

   **AND**

   b. **Relapsed** (appearance of a new lesion or ≥50% increase in size of previously involved sites after a complete response) or **refractory** (≥50% increase from nadir in the size of any abnormal lesion or appearance of a new lesion during or following initial treatment) disease defined by at least **ONE** of the following:
      o Unable to achieve a complete remission following second line of systemic chemotherapy; **OR**
      o Disease is in second or greater relapse/recurrence; **OR**
      o Relapsed after autologous hematopoietic stem cell transplantation (HSCT); **OR**
      o Relapsed transplant ineligible disease.

   **AND**

   c. Member has received **TWO or more lines** of systemic chemotherapy (which may or may not include therapy supported by stem cell transplant):
      o Anti-CD20 monoclonal antibody (e.g., rituximab), UNLESS the tumor is CD20 negative or the member has a FDA-labeled contraindication to anti-CD20 therapy; **OR**
      o An anthracycline-containing chemotherapy regimen; **OR**

   **Informational Note:** ZUMA-1 trial included only patients that received prior anti-CD20 antibody therapy and an anthracycline-containing regimen.
      o For Transformed Follicular Lymphoma: Prior chemotherapy for FL with chemotherapy refractory disease after transformation to DLBCL.

   **OR**

2. **Definitive diagnosis of R/R FL** met by **ALL** of the following (a-c):
   a. Histologically confirmed diagnosis of indolent follicular lymphoma; **AND**
   b. R/R indolent follicular lymphoma (grades 1-3a); **AND**
   c. Disease progression after **TWO or more prior lines** of treatment that included an anti-CD20 monoclonal antibody plus an alkylating agent.
AND

B. Member meets ALL of the following (1-6):

1. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.  
   **NOTE:** ECOG performance status of 2 or greater does not meet criterion.

AND

2. Documentation of ALL of the following clinical findings:
   a. Absolute neutrophil count (ANC) ≥ 1000/uL; **AND**
   b. Absolute lymphocyte count (ALC) > 100/uL; **AND**
   c. Platelet count ≥ 75,000/uL

AND

3. Adequate bone marrow, cardiac, pulmonary, and organ function with no deterioration expected within 4 weeks after Yescarta infusion, as determined by the treating oncologist/hematologist and supported by the following labs:
   a. Platelet count ≥ 75,000/Ul; **AND**
   b. Absolute neutrophil count (ANC) ≥ 1000/uL; **AND**
   c. Absolute lymphocyte count (ALC) > 100/uL.

   **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.

AND

4. Confirmation/attestation of ALL of the following:
   a. Member will not receive ANY of the following:
      o A G-CSF agent within the first 3 weeks after Yescarta infusion or until CRS has resolved; **AND**
      **Informational Note:** Myeloid growth factors, particularly GM-CSF, are not recommended during the first 3 weeks after CAR T cell infusion or until CRS has resolved. (Kansagra et al. 2019) 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 (Yáñez L et al. 2019; Santomasso et al. 2018)
      o Live virus vaccine for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during Yescarta treatment and **until immune recovery** following treatment with Yescarta.
   b. For members with a history of allogeneic stem cell transplant: Documentation (e.g., recent chart notes) confirming that member has no signs of active graft versus host disease (GVHD)
   c. Member has not received, or is being considered for CAR-T therapy, other gene therapy, or other investigational cellular therapy for cancer
   d. For women of reproductive potential:
      o Member is not pregnant or breast-feeding: Negative serum pregnancy test within the past 30 days; **AND**
      o Member has been counseled on the use of effective contraception during treatment.

AND

5. 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

6. Current weight for review of prescribed dosage
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.

Repeat administration of CAR-T cell is experimental and investigational since the safety and efficacy beyond ONE treatment 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.

LIMITATIONS AND EXCLUSIONS
There are no contraindications listed in the manufacturer’s labeling at this time. The following are considered exclusions based on insufficient evidence:

1. Prior treatment, or being considered for treatment, with CAR-T therapy or other gene therapy; OR repeat treatment with Yescarta
2. Pregnancy: Not recommended for women who are pregnant, and pregnancy after Yescarta infusion should be discussed with the treating physician
   Informational Note: It is not known if Yescarta has the potential to be transferred to the fetus and is not recommended for women who are pregnant.
3. Active hepatitis B virus (HBSAg positive) or active hepatitis C virus (anti-HCV positive) if viral load is detectable; Human immunodeficiency virus (HIV) positive. NOTE: A history of hepatitis B or hepatitis C is permitted if the viral load is undetectable per quantitative PCR and/or nucleic acid testing.
4. Active, uncontrolled infections (fungal, bacterial, viral, or other uncontrolled infections); Uncontrolled or requires IV antimicrobials (antibiotics, antifungals, antiprotozoals, antivirals).
5. Active inflammatory disorders
6. Active GVHD
7. Presence or history of:
   a. Active or primary CNS disease; detectable cerebrospinal fluid malignant cells or brain metastases;
   b. Presence or history of: Primary CNS lymphoma or CNS disorder such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement [Informational Note: NCCN guidelines define CNS involvement (CNS leukemia CNS-3) as the following: WBC count of ≥ 5 leukocytes/mcL in the CSF with the presence of lymphoblasts]

The following are considered experimental, investigational and unproven based on insufficient evidence:

1. Any indications other than those listed above
   Based on the peer-reviewed medical literature the safety and effectiveness for indications other than the medically necessary indication listed above has not been established.
2. Prior treatment with CAR T-cell therapy, any other gene therapy, or is being considered for treatment with any other gene therapy

DURATION OF APPROVAL: Duration sufficient for ONE single course of treatment.

PRESCRIBER REQUIREMENTS: Prescribed by, or in consultation with, an oncologist/hematologist at a certified treatment center

AGE RESTRICTIONS: 18 years of age or older at time of infusion

Pediatric patients: The safety and efficacy in pediatric patients have not been established.

DOSING CONSIDERATIONS: R/R LBCL and R/R FL: A treatment course consists of lymphodepleting chemotherapy (with fludarabine and cyclophosphamide) on the 5th, 4th, and 3rd day prior to Yescarta infusion.

- Target dose is 2 x 10^6 CAR-positive viable T cells per kg body weight, not to exceed 2 x 10^8 CAR-positive viable T cells. Confirm availability of autologous Yescarta prior to initiating lymphodepleting chemotherapy.
- Pre-treatment: A lymphodepleting chemotherapy regimen of 3 doses of cyclophosphamide and fludarabine infused intravenously on 5th, 4th, and 3rd day before infusion of Yescarta: Fludarabine 30 mg/m^2 IV daily for 3 days; Cyclophosphamide 500 mg/m^2 IV daily for 3 days starting with the first dose of fludarabine.
• Premedication (acetaminophen and diphenhydramine) is required prior to Yescarta infusion. Ensure tocilizumab and emergency equipment are available prior to infusion and during recovery period.

MONITORING PARAMETERS:
• Monitor for signs/symptoms of Cytokine Release Syndrome (CRS), Neurologic Toxicities [BOXED WARNINGS]
• Screen for hepatitis B virus (HBV), hepatitis C virus, and HIV in accordance with clinical guidelines prior to collection of cells for manufacturing. The American Society of Clinical Oncology HBV screening and management provisional clinical opinion (ASCO [Hwang 2020]) recommends HBV screening with hepatitis B surface antigen, hepatitis B core antibody, total Ig or IgG, and antibody to hepatitis B surface antigen prior to beginning (or at the beginning of) systemic anticancer therapy; do not delay treatment for screening/results. Detection of chronic or past HBV infection requires a risk assessment to determine antiviral prophylaxis requirements, monitoring, and follow-up.

QUANTITY LIMITATIONS: ONE (1) single treatment course of Yescarta for lifetime

Concurrent Authorizations: Authorizations for Yescarta will also receive approval of Actemra (tocilizumab). Max 8 single dose vials per lifetime [Refer to Actemra (tocilizumab) Policy No: C10265-A].

Informational Note: Actemra is indicated for the treatment of CAR T cell-induced severe or life-threatening CRS in patients ≥ 2 years of age. According to the FDA approved labeling for intravenous tocilizumab, the dose should not exceed 800 mg per infusion every 4 weeks for RA or CRS patients (Actemra Prescribing Information, 2020).

ADMINISTRATION:
1. Yescarta is considered a provider-administered therapy under the expertise and safety measures available in certified treatment centers enrolled in the REMS program
   • Certified healthcare facilities must have on-site, immediate access to tocilizumab.
   • 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 on the management of CRS and neurologic toxicities.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud, waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DRUG INFORMATION

ROUTE OF ADMINISTRATION: Intravenous Infusion

DRUG CLASS: Antineoplastic Agent, Anti-CD19; Antineoplastic Agent, Chimeric Antigen Receptor (CAR) T Immunotherapy; CAR-T Cell Immunotherapy; Cellular Immunotherapy, Autologous.

FDA-APPROVED USES: Follicular Lymphoma, relapsed or refractory (R/R FL): Treatment of relapsed or refractory follicular lymphoma in adults after ≥ 2 lines of systemic therapy (FDA approval: March 5, 2021)

Large B-cell lymphoma, relapsed or refractory (R/R LBCL): Treatment of R/R LBCL in adults after ≥ 2 lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal LBCL, high-grade B-cell
lymphoma, and DLBCL arising from follicular lymphoma (FDA approval: October 18, 2017)

Limitations of use: Not indicated for the treatment of patients with primary central nervous system (CNS) lymphoma

COMPENDIAL APPROVED OFF-LABELED USES: None

RISK EVALUATION AND MITIGATION STRATEGY (REMS): Available only through the Yescarta and Tescartus REMS program due to the serious risks of CRS and neurologic toxicities.

BOXED WARNING: CRS; Neurologic Toxicities

### SUMMARY OF MEDICAL EVIDENCE

**Large B-cell Lymphoma, Relapsed or Refractory**

The FDA approved the use of Yescarta for the treatment of patients with relapsed or refractory aggressive B-cell NHL based on the results from the ZUMA-1 clinical trial (Neelapu et al., 2017).

**ZUMA-1** is a single-arm, open-label, multi-center Phase 2 trial with large B-cell NHL (DLBCL, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma) who had previously received two treatments. Eligible patients had refractory disease or relapsed after autologous stem-cell transplantation; an ECOG performance status of 0 or 1; had previously received an anti-CD20 monoclonal antibody containing-regimen and an anthracycline-containing chemotherapy.

- 111 patients enrolled; 101 patients received Yescarta (N=101); median age: 58 years (range 23 to 76 years)
  - Yescarta was manufactured for 110 patients and administered to 101 patients [1 patient was excluded due to unsuccessful manufacturing; 7 patients were excluded due to adverse events and/or tumor progression and 2 patients due to non-measurable disease]
- 77 patients with DLBCL, 8 patients with PMBCL, 16 patients with TFL; 85% had stage III or IV disease
- 69% of patients had received at least 3 prior lines of therapy; 77% had refractory disease to a second or greater line of therapy, and 21% had relapsed within 1 year of autologous HSCT
- Yescarta was administered as a single intravenous infusion at a target dose of $2 \times 10^6$ CAR-positive viable T cells/kg (maximum permitted dose: $2 \times 10^8$ cells). The lymphodepleting regimen consisted of cyclophosphamide 500 mg/m² intravenously and fludarabine 30 mg/m² intravenously, both given on the 5th, 4th, and 3rd day before Yescarta. Bridging chemotherapy between leukapheresis and lymphodepleting chemotherapy was not permitted.
- The median turnaround time for production of Yescarta was 17 days. All patients were hospitalized for Yescarta infusion and for a minimum of 7 days afterward.
- Results:
  - Among the 101 patients receiving Yescarta, the objective response rate was 82%. Complete response was observed in 54%. At a median follow up of 27.1 months, 83% of patients had a response and 58% had a complete response.
  - Median time to response was observed to be 1 month (range: 0.8–6 months)
  - Median duration of response of 8.1 months
  - Grade 3 or higher adverse events occurred in 95% of patients; neutropenia (78%), anemia (43%), and thrombocytopenia (38%) were the most common.
  - 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. 3 patients died during treatment; 2 deaths were related to Yescarta.
Long-term safety and activity of Yescarta in refractory LBCL (ZUMA-1): a single-arm, multicenter, phase 1-2 trial (Locke FL et al. 2019)

- After a median follow-up of 27.1 months in 101 patients from the ZUMA-1 study, Yescarta resulted in an objective response rate of 83% and 58% had a complete response. Median duration of response was 11.1 months.
- Median overall survival was not reached (12.8 to not estimable), with an estimated 24-month survival of 50.5% and the median progression-free survival 5.9 months.
- In patients with double-expressor and high-grade B-cell lymphoma (n=33), an objective response rate occurred in 91% including a complete response in 70%.
- Grade 3 or worse events occurred in 98% of patients. Grade 3 or worse CRS (11%) and neurological events (32%) were manageable and mostly reversible.
- This 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 R/R LBCL.

Four-year follow-up data from the pivotal ZUMA-1 trial of Yescarta in adult patients with refractory LBCL was reported at the American Society of Hematology (ASH) Annual Meeting and Exposition (Abstract #1187):

- Of 111 patients enrolled in the ZUMA-1 Phase 2 cohorts, Yescarta was administered to 101 patients with refractory LBCL, and the median time from leukapheresis to complete response was less than two months.
- There have been no Yescarta-related secondary malignancies reported and the four-year overall survival rate was 44%.

**Follicular Lymphoma, relapsed or refractory (R/R FL)**

The accelerated FDA approval was supported by data from the primary analysis of the Phase 2 ZUMA-5 trial. ZUMA-5 is a single-arm, multicenter, open-label Phase 2 study that aims to enroll up to 160 adult patients (≥18 years old) with relapsed or refractory indolent NHL of either FL or marginal zone lymphoma (MZL) subtypes, who received at least two prior lines of systemic therapy, including an anti-CD20 monoclonal antibody combined with an alkylating agent.

ZUMA-5 is evaluating 146 adult patients (124 FL; 22 MZL) treated with Yescarta following two or more prior lines of therapy, including the combination of an anti-CD20 monoclonal antibody and an alkylating agent. The objectives of the study are to evaluate the efficacy and safety of a single infusion of Yescarta in this patient population. The primary endpoint of the trial is objective response rate as assessed by an independent review committee. Secondary endpoints include complete response rate, duration of response, progression-free survival, overall survival, safety and CAR T cell and cytokines levels. The study is ongoing.

- The most recent efficacy results of the trial showed 91% of patients with R/R FL (n=81) responded to one infusion of Yescarta and approximately 74% of patients in a continued remission at 18 months. This included 60% of patients who achieved a complete remission, and 13 of the 25 patients who achieved a partial remission also met imaging criteria for a complete remission but had not been confirmed by a negative bone marrow biopsy after treatment.
- Median duration of response among all patients with FL had not been reached at median follow-up of 14.5 months.
- 21% of patients experienced grade 3 or worse neurologic side effects and 8% experienced CRS.
- The median time to onset of CRS was 4 days (range, 1-15) and the median duration of events was 6 days (range, 1-27). 99% of patients, however, had resolved events.
- The most common (≥10%) grade 3 or higher adverse reactions included febrile neutropenia, encephalopathy, and infections with pathogen unspecified.
- **Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).**
- Estimated Primary Completion Date: February 2022
Hayes. A Precision Therapy Assessment, Axicabtagene Ciloleucel (Yescarta) for Treatment of Relapsed or Refractory B-Cell Malignancies, was published Dec 11, 2020. The report notes that Yescarta is a treatment option for a patient population that generally has a poor prognosis; however, while there are favorable survival outcomes based on the data available, additional data are required to confirm these findings and provide a comparative context. The assessment concluded there is insufficient evidence to determine the relative efficacy and safety of Yescarta therapy among adult patients with R/R LBCL. The report notes there is substantial uncertainty regarding the safety and effectiveness of Yescarta therapy, due primarily to a lack of comparative studies and long-term follow-up data.

National and Specialty Organizations

National Comprehensive Cancer Network (NCCN) developed guidelines for the treatment of B-cell lymphoma with the following recommendation:

Axicabtagene ciloleucel is indicated for the treatment of adult patients with r/r LBCL after ≥ 2 lines of systematic therapy, including DLBCL (not otherwise specified), high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. Several level 2A recommendations (based upon lower-level evidence and uniform NCCN consensus that the intervention is appropriate) are provided for the specific use of axicabtagene ciloleucel within clinical decision-making charts. (NCCN B-Cell Lymphomas Guidelines)

National Institute for Health and Care Excellence (NICE) published a technology appraisal guidance ‘Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies’ [TA559]. NICE recommends axicabtagene ciloleucel therapy for use within the Cancer Drugs Fund as an option for treating R/R DLBCL or PMLBCL in adults after 2 or more systemic therapies, if conditions in the managed access agreement are followed (NICE 2019).

The Institute for Clinical and Economic Review (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.

SUPPLEMENTAL INFORMATION

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.

Chimeric Antigen Receptor T-cells (CAR T-cells): T-cells that have been genetically altered in order to improve the ability of the T-cells to fight cancer. The genetic modification creates a new and special receptor on the surface of the T-cell. This special receptor is called a CAR and there are many CARs on the surface of the T-cell. CAR enhances the ability of the T-cell to recognize and attach to a specific protein, called an antigen, on the surface of a cancer cell. (CMS)

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 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.

Cytokine release syndrome (CRS): An acute systemic inflammatory response syndrome characterized by fever, with or without multiple organ dysfunction that is associated with CAR-T cell therapy or other forms of immunotherapy. Clinical manifestations include fever, which may be accompanied by fatigue, headache, rash, diarrhea, arthralgia, and myalgia. Milder CRS can progress to a more severe syndrome, which may include hypotension, hypoxia, and uncontrolled systemic inflammatory response with circulatory collapse, vascular leakage, peripheral and/or pulmonary edema, renal failure, cardiac dysfunction, and multiorgan system failure.

Eastern Cooperative Oncology Group Performance Status (ECOG-PS)
A scale used to determine the individual's level of functioning; standard criteria for measuring how the disease impacts a patient's daily living abilities

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
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<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>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</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Deceased</td>
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The scale was developed by the ECOG, now part of the ECOG-ACRIN Cancer Research Group and published in 1982.

Outcomes Measures in Clinical Trials
- Objective response rate (ORR) is defined as the incidence of a CR or a PR per the Lugano Classification (Cheson et al, 2014), as determined by the Independent Radiology Review Committee (IRRC).
- Duration of response (DOR) is defined as the time from their first objective response to disease progression or death.
- Best objective response is defined as the incidence of CR, PR, SD, progressive disease, or unevaluable as best response to treatment
- Progression free survival (PFS) is defined as the time from the anti-CD19 CAR T cells infusion date to the date of disease progression or death from any cause
- Overall Survival (OS): Percentage of participants experiencing treatment-emergent adverse events; Percentage of participants who had clinically significant changes in laboratory values.

Refractory NHL is NHL that has not responded to initial treatment. Refractory disease may be disease that is getting worse or staying the same.

Relapsed NHL is NHL that responded to treatment but then returns.

**CODING & BILLING INFORMATION**

<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
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<tbody>
<tr>
<td>0537T</td>
<td>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</td>
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<tr>
<td>0538T</td>
<td>Chimeric antigen receptor T-cell (CAR-T) therapy; preparation of blood-derived T lymphocytes for transportation (eg, cryopreservation, storage)</td>
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<tr>
<td>0539T</td>
<td>Chimeric antigen receptor T-cell (CAR-T) therapy; receipt and preparation of CAR-T cells for administration</td>
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<td>0540T</td>
<td>Chimeric antigen receptor T-cell (CAR-T) therapy; CAR-T cell administration, autologous</td>
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**HCPCS**  **Description**

Molina Clinical Policy
Yescarta (axicabtagene ciloleucel)
Policy No. 396
Last Approval: 6/7/2021
Next Review Due By: June 2022
Q2041 | Axicabtagene Ciloleucel, up to 200 million autologous Anti-CD19 CAR T Cells, including leukapheresis and dose preparation procedures, per infusion

AVAILABLE DOSAGE FORMS: A suspension for intravenous infusion. Each single infusion bag of Yescarta contains a suspension of CAR-positive T cells in approximately 68 mL.

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>MAC</th>
<th>Description</th>
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<tr>
<td>4/12/2018</td>
<td>MCP</td>
<td>New policy. IRO Peer Review: 11/21/2017. Practicing physician board certified in Internal Medicine, Oncology, Hematology.</td>
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<td>3/11/2020</td>
<td>MCP</td>
<td>Policy revised. IRO Peer Review: Practicing physician board certified in Oncology, Hematology. Notable revisions include:</td>
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<td>4/23/2020</td>
<td>MCP</td>
<td>Policy revised. IRO Peer Review: 3/31/2020. Practicing physician board certified in Oncology, Hematology. Notable revisions include:</td>
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<td>2/8/2021</td>
<td>MCP</td>
<td>Policy reviewed and updated. No changes in coverage criteria. Content updates and revisions include:</td>
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<tr>
<td>6/7/2021</td>
<td>MCP</td>
<td>Policy revised. IRO Peer Review: Policy was reviewed by practicing physician board certified in Oncology, Hematology, 5/9/2021. Notable revisions include:</td>
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<tr>
<td>9/2021</td>
<td></td>
<td>Policy converted to new template in Sep 2021.</td>
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REFERENCES

Government Agency

ClinicalTrials.gov.

U.S. Food and Drug Administration (FDA)
- Summary Basis for Regulatory Action for Yescarta (BLA125643). 2017; Available at: [Link](https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm771022.htm) Accessed April 2021.


Prescribing Information and Drug Compendia

Yescarta (axicabtagene ciloleucel) [prescribing information]. Santa Monica, CA: Kite Pharma, Inc; March 2021.


Peer Reviewed Publications


National and Specialty Organizations


The Leukemia & Lymphoma Society (LLS)


• Treatment for Indolent Subtypes. Available at: [Link] Accessed April 2021

Other Peer Reviewed and Professional Organization Publications (used in the development of this policy)

DynaMed [Internet]. Ipswich (MA): EBSCO Information Services. 1995 -. Record No. T116014, Non-Hodgkin Lymphoma (NHL); [updated 2018 Dec 03, cited March 2020]. Available at: https://www.dynamed.com/topics/dmp~AN~T116014. Registration and login required


UpToDate [website]: Waltham, MA: Wolters Kluwer Health; 2021. Registration and login required

• Treatment of Relapsed or Refractory Diffuse Large B Cell Lymphoma. Topic 4708 Version 71.0. Topic last updated Aug 3, 2020

• Histologic Transformation of Follicular Lymphoma. Topic 4724 Version 32.0. Topic last updated October 2, 2020

APPENDIX

Reserved for State specific information (to be provided by the individual States, not Corporate). Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.

Centers for Medicare & Medicaid Services (CMS)
On August 7th, 2019 CMS published a National Coverage Determination (NCD) regarding CAR-T therapy coverage in the Medicare program. According to the NCD, for services performed on or after August 7, 2019, CMS covers autologous 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. (Rev. 10454, Issued: 11-13-20, Effective: 08-07-19, Implementation: 02-16-21)

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)]