



<b>Guideline</b>	Chimeric Antigen Receptor T Cell Therapy (CAR-T Therapy): (tisagenlecleucel) and (axicabtagene ciloleucel)	<b>Guideline #</b>	UM_OTH 21
		<b>Original Effective Date</b>	5/13/2020
<b>Section</b>	Other	<b>Revised Date</b>	

## COVERAGE POLICY

### Kymriah (tisagenlecleucel)

#### Coverage criteria:

- A. Confirmed CD19-positive B-cell acute lymphoblastic leukemia with morphologic bone marrow tumor involvement ( $\geq 5\%$  lymphoblasts); and
- B. 25 years or younger at time of infusion
- C. No prior treatment with Kymriah or any other gene therapy or are not being considered for treatment with any other gene therapy; and
- D. Adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis; and
- E. Kymriah will be dispensed and administered at a Risk Evaluation and Mitigation Strategy (REMS) certified facility
  1. Healthcare facilities that dispense and administer Kymriah must provide documentation of certification in the REMS program.
  2. Certified healthcare facilities must ensure that hematologists/oncologists who prescribe, dispense or administer Kymriah are trained about the management of cytokine release syndrome (CRS) and neurologic toxicities.
- F. Pre-Treatment: confirm availability of Kymriah prior to starting the lymphodepleting regimen:
  1. Lymphodepleting chemotherapy: Fludarabine (30 mg/m<sup>2</sup> intravenous daily for 4 days) and cyclophosphamide (500 mg/m<sup>2</sup> intravenous daily for 2 days starting with the first dose of fludarabine).
  2. Infuse KYMRIA 2 to 14 days after completion of the lymphodepleting chemotherapy.
  3. Ensure that 2 doses of tocilizumab and emergency equipment are available prior to infusion and during the recovery period.



- G. Post-Treatment: monitor patients 2-3 times during the first week following Kymriah infusion at the certified healthcare facility for signs and symptoms of CRS and neurologic toxicities, monitor patients for signs or symptoms of CRS for at least 4 weeks after treatment with KYMRIA.
    - 1. Instruct patients to remain within proximity of the certified healthcare facility for at least 4 weeks following infusion.
  - H. ONE (1) single-dose of Kymriah is approved per lifetime.
- 

**Yescarta** (axicabtagene ciloleucel) and **Kymriah** (tisagenlecleucel)

---

**Coverage criteria**

- A. A diagnosis of diffuse large B-cell lymphoma, not otherwise specified; or primary mediastinal large B-cell lymphoma or high-grade B-cell lymphoma or diffuse large B-cell lymphoma arising from follicular lymphoma; and
- B. 18 years or older at time of infusion, and
- C. Prior therapy including all of the following:
  - 1. Anti-CD20 monoclonal antibody for CD20-positive tumor
  - 2. Anthracycline-containing chemotherapy regimen
  - 3. For subjects with transformed follicular and subsequently have chemorefractory disease after transformation to diffuse large B-cell lymphoma
- D. Adequate organ and bone marrow function as determined by the treating oncologist/hematologist; and
- E. Have not received prior CD19-directed CAR-T cell therapy treatment or any other gene therapy or are being considered for treatment with any other gene therapy; and
- F. Yescarta and Kymriah will be dispensed and administered at a Risk Evaluation and Mitigation Strategy (REMS) certified facility
  - 1. Healthcare facilities that dispense and administer Kymriah or Yescarta must provide documentation of certification in the REMS program.
  - 2. Certified healthcare facilities must ensure that hematologists/oncologists who prescribe, dispense or administer Kymriah or Yescarta are trained about the management of CRS and neurologic toxicities.
- G. Pre-treatment: confirm availability of Kymriah or Yescarta prior to starting the lymphodepleting regimen.
  - 1. Kymriah lymphodepleting chemotherapy: Fludarabine (25 mg/m<sup>2</sup> i.v. daily for 3 days) and cyclophosphamide (250mg/m<sup>2</sup> IV daily for 3 days starting with the first dose of fludarabine). Infuse Kymriah 2 to 11 days after completion of the lymphodepleting chemotherapy.



- a. Lymphodepleting chemotherapy may be omitted if a patient's white blood cell (WBC) count is less than or equal to  $1 \times 10^9/L$  within 1 week prior to Kymriah infusion.
  2. Yescarta lymphodepleting chemotherapy: Administer a lymphodepleting chemotherapy regimen of cyclophosphamide  $500 \text{ mg/m}^2$  intravenously and fludarabine  $30 \text{ mg/m}^2$  intravenously on the fifth, fourth, and third day before infusion of Yescarta. Infuse Yescarta 3 days after completion of the completion of the lymphodepleting chemotherapy.
  3. Ensure that 2 doses of tocilizumab are available prior to infusion of Kymriah or Yescarta
- H. Post-treatment: monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS and neurologic toxicities.
1. Instruct patients to remain within proximity of the certified healthcare facility for at least 4 weeks following infusion.
- I. ONE (1) single-dose of Kymriah per lifetime OR ONE (1) single-dose of Yescarta is approved per lifetime

#### **COVERAGE LIMITATION AND EXCLUSIONS**

- A. Kymriah (tisagenlecleucel) is not FDA-approved for relapse or refractory primary mediastinal large B-cell lymphoma
- B. Kymriah should not be used in the presence of the following:
  1. Burkitt lymphoma
  2. Active hepatitis B, C, or any uncontrolled infection
  3. Grade 2 to 4 graft-versus-host disease
  4. Concomitant genetic syndrome with the exception of Down syndrome
  5. Allogeneic cellular therapy, such as donor lymphocyte infusion, within 6 weeks prior to Kymriah infusion
  6. Active central nervous system 3 (CNS 3) acute lymphoblastic leukemia (ie, white blood cell count  $\geq 5$  cells/microliter in cerebrospinal fluid with presence of lymphoblasts).
- C. Yescarta and Kymriah are not indicated for treatment of primary central nervous system lymphoma
- D. Kymriah and Yescarta have black box warnings because of the risks of cytokine release syndrome (CRS) and neurologic toxicities, including fatal or life-threatening reactions, occurring in patients receiving Kymriah or Yescarta. Patients must be monitored for neurologic toxicities after treatment with Kymriah or Yescarta.
- E. Kymriah or Yescarta should not be administered to patients with active infection.
- F. Pregnancy: Kymriah and Yescarta are excluded in pregnancy. There are no available data with Kymriah and Yescarta use in pregnant women. No animal reproductive and



developmental toxicity studies have been conducted with Kymriah or Yescarta to assess whether these medications can cause fetal harm when administered to a pregnant woman. It is not known if Kymriah or Yescarta have the potential to be transferred to the fetus.

- G. Pediatric patients: Kymriah is excluded in children who are younger than age 3 years. Clinical studies of Kymriah included patients who were 3 years of age to 25 years of age; The safety and efficacy of Yescarta has not been established in pediatric patients; therefore Yescarta is excluded in the pediatric population.
- H. Geriatric patients: The safety and effectiveness of Kymriah and Yescarta have not been established in geriatric patients. Clinical studies of Kymriah and Yescarta for this indication did not include patients age 65 years and over.

**ADDITIONAL INFORMATION**

Axicabtagene ciloleucel and tisagenlecleucel are created from the patient’s own T cells which are withdrawn from the patient, genetically engineered to target the CD19 antigen on B cells and then given back to the patient intravenously. This process of using the immune system’s natural fighting ability is called adoptive immunotherapy.

Applicable Codes

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement policy.

HCPCS Code	Description
Q2041	Axicabtagene ciloleucel (Yescarta), up to 200 million autologous anti-CD19 car positive viable T cells, including leukapheresis and dose preparation procedures, per therapeutic dose
Q2042	Tisagenleelucel (Kymriah), up to 600 million car-positive viable T cells, including leukapheresis and dose preparation procedures, per therapeutic dose

**CLINICAL/REGULATORY RESOURCE**

- A. Medicare
  - 1. The Centers for Medicare and Medicaid Services (CMS) covers CAR T-cell therapy when administered at facilities enrolled in the REMS program and is used for either an FDA-approved indication or when the product is FDA approved and the use is supported in one or more CMS-approved compendia.
- B. Medi-Cal
  - 1. The Medi-Cal Provider Manual contains information on authorization requirements for chemotherapy. Both axicabtagene ciloleucel and tisagenlecleucel are included in



a section which lists specific medications regarding policy related to billing for injection services.

C. MCG Health

1. No references available on CAR-T cell therapy.

D. Apollo Managed Care

1. Guideline only states that health plans are exploring potential coverage.

E. National Comprehensive Cancer Network Guidelines (NCCN)

1. Acute Lymphoblastic Leukemia:

- a. Recommends (category 2A) Kymriah (tisagenlecleucel) as a treatment for:
  - i. Philadelphia chromosomes-positive patients less than 26 years in age with refractory disease or 2 or more relapses and failure of 2 tyrosine kinase inhibitors.
  - ii. Philadelphia chromosome-negative patients less than 26 years in age with refractory disease or 2 or more relapses.

2. B-cell Lymphomas:

- a. Recommends (category 2A) Yescarta (axicabtagene ciloleucel) or Kymriah (tisagenlecleucel) as a treatment option for:
  - i. Histological transformation to diffuse large B-cell lymphoma after multiple lines of prior therapies which include  $\geq 2$  chemo-immunotherapy regimens for indolent or transformed disease.
  - ii. Relapsed or refractory diffuse large B-cell lymphoma after multiple lines of prior therapies which include  $\geq 2$  chemo-immunotherapy regimens for indolent or transformed disease.

## DEFINITION OF TERMS

1. Relapse disease is defined as the reappearance of leukemia cells in the bone marrow or peripheral blood after the attainment of a complete remission with chemotherapy and/or allogeneic cell transplant.
2. Refractory (resistant) disease is defined as those patients who fail to obtain complete response with induction therapy, i.e., failure to eradicate all detectable leukemia cells (<5% blasts) from the bone marrow and blood with subsequent restoration of normal hematopoiesis (>25% marrow cellularity and normal peripheral blood counts).
3. Risk Evaluation and Mitigation Strategies (REMS)- drug safety program that the FDA can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risk.
4. Central nervous system (CNS) disease for B-cell acute lymphoblastic leukemia is defined by the following groups:
  - A. CNS 1: Absence of blasts on cerebrospinal fluid cytospin preparation, regardless of the white blood cell (WBC) count
  - B. CNS 2: WBC count of less than 5/mL and blasts on cytospin findings



- C. CNS 3: WBC count of 5/mL or more and blasts on cytospin findings and/or clinical signs of CNS leukemia (e.g, facial nerve palsy, brain/eye involvement, hypothalamic syndrome)

## REFERENCES

1. Apollo Managed Care, 19<sup>th</sup> edition, 7<sup>th</sup> Online edition, 2020. HO 153 CAR-T Cancer Immunotherapy.
2. California Department of Health Care Services. 2019. Medi-Cal Provider Manual. Chemotherapy: Drugs A-D Policy
3. The Centers for Medicare and Medicaid Services (CMS). Decision Memo for Chimeric Antigen Receptor (CAR) T-cell Therapy for Cancers (CAG-00451N). August 7, 2019. Accessed May 6, 2020 at <https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=291>.
4. KYMRIAH (tisagenlecleucel) FDA approval and Labeling Information accessed at: <https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/ucm573706.htm>. Accessed on March 27, 2020.
5. Maude SL, Frey N, Shaw PA et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med*. 2014 Oct 16;371(16):1507-17. doi: 10.1056/NEJMoa1407222.
6. Maude SL, Laetsch TW, Buechner J et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. *N Engl J Med*. 2018 Feb 1;378(5):439-448. doi: 10.1056/NEJMoa1709866.
7. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: acute lymphoblastic leukemia. Version 1.2020. [https://www.nccn.org/professionals/physician\\_gls/pdf/all.pdf](https://www.nccn.org/professionals/physician_gls/pdf/all.pdf). Accessed on March 27, 2020.
8. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: B-Cell lymphomas. Version 1.2020. [https://www.nccn.org/professionals/physician\\_gls/pdf/b-cell.pdf](https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf). Accessed on March 27, 2020.
9. YESCARTA™ (axicabtagene ciloleucel) FDA approval and Labeling Information accessed at: <https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/ucm581222.htm>. Accessed on March 27, 2020.



## **DISCLAIMER**

IEHP Clinical Authorization Guidelines (CAG) are developed to assist in administering plan benefits, they do not constitute a description of plan benefits. The Clinical Authorization Guidelines (CAG) express IEHP's determination of whether certain services or supplies are medically necessary, experimental and investigational, or cosmetic. IEHP has reached these conclusions based upon a review of currently available clinical information (including clinical outcome studies in the peer-reviewed published medical literature, regulatory status of the technology, evidence-based guidelines of public health and health research agencies, evidence-based guidelines and positions of leading national health professional organizations, view of physicians practicing in relevant clinical areas, and other relevant factors). IEHP makes no representations and accepts no liability with respect to the content of any external information cited or relied upon in the Clinical Authorization Guidelines (CAG). IEHP expressly and solely reserves the right to revise the Clinical Authorization Guidelines (CAG), as clinical information changes.