Introduction

The immune system is made up of several different disease-fighting cells. In cancer, however, the immune system sometimes either doesn’t work as it should, or the cancer cells are able to hide from the immune system. One therapy that draws on the immune system’s natural fighting ability is called adoptive immunotherapy. In this technique, certain types of immune system cells are withdrawn from the person to be treated. They’re re-engineered in a lab and given back to the patient in the hope that they will be better able to attack and defeat cancer cells. This is an active area of study. The U.S. Food and Drug Administration has approved two adoptive immunotherapy treatments, Kymriah™ (tisagenlecleucel) and Yescarta™ (axicabtagene ciloleucel). The FDA has approved them for people of certain ages who have specific types of cancer. This policy describes when these treatments may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
**Policy Coverage Criteria**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kymriah™ (tisagenlecleucel)</strong></td>
<td><strong>Kymriah™ (tisagenlecleucel) intravenous infusion is considered medically necessary for relapsed(^a) or refractory(^b) patients if they meet all of the following criteria:</strong></td>
</tr>
<tr>
<td></td>
<td>- Confirmed diagnosis of CD19-positive B-cell acute lymphoblastic leukemia with morphologic bone marrow tumor involvement (≥5% lymphoblasts)</td>
</tr>
<tr>
<td></td>
<td>- Are up to 25 years old at the time of infusion</td>
</tr>
<tr>
<td></td>
<td>- Have not received prior treatment with tisagenlecleucel or any other gene therapy or are being considered for treatment with any other gene therapy</td>
</tr>
<tr>
<td></td>
<td>- Have adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis</td>
</tr>
<tr>
<td></td>
<td>- Do not have any of the following:</td>
</tr>
<tr>
<td></td>
<td>- Burkitt lymphoma</td>
</tr>
<tr>
<td></td>
<td>- Active hepatitis B, C, or any uncontrolled infection</td>
</tr>
<tr>
<td></td>
<td>- Grade 2 to 4 graft-versus-host disease</td>
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<tr>
<td></td>
<td>- Concomitant genetic syndrome with the exception of Down syndrome</td>
</tr>
<tr>
<td></td>
<td>- Received allogeneic cellular therapy, such as donor lymphocyte infusion, within 6 weeks prior to tisagenlecleucel infusion</td>
</tr>
<tr>
<td></td>
<td>- Patient has active central nervous system 3 (see <strong>Related Information</strong>) acute lymphoblastic leukemia (ie, white blood cell count ≥5 cells/μL in cerebrospinal fluid with presence of lymphoblasts).</td>
</tr>
</tbody>
</table>

**Note:**

\(^a\) Relapsed disease describes 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.

\(^b\) Refractory (resistant) disease is defined as those patients who fail to obtain complete response with induction therapy, ie, 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).
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| Yescarta™ (axicabtagene ciloleucel) | Yescarta™ (axicabtagene ciloleucel) or Kymriah™ (tisagenlecleucel) intravenous infusion (except as indicated) is considered medically necessary for relapsed or refractory patients if they meet all of the following criteria:  
  • Are adults (age ≥18) at the time of infusion  
  • Histologically confirmed 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  
  • Received adequate prior therapy including all of the following:  
    o Anti-CD20 monoclonal antibody for CD20-positive tumor  
    o Anthracycline-containing chemotherapy regimen  
    o For subjects with transformed follicular lymphoma, prior chemotherapy for follicular lymphoma and subsequently have chemorefractory disease after transformation to diffuse large B-cell lymphoma  
      ▪ Have adequate organ and bone marrow function as determined by the treating oncologist/hematologist  
      ▪ 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  
  • Do not have primary central nervous system lymphoma |
| Kymriah™ (tisagenlecleucel) | Note:  
  c Tisagenlecleucel intravenous infusion is considered investigational for the treatment of relapsed or refractory primary mediastinal large B-cell lymphoma. |
| Treatment | Investigational |
| Other applications | Other applications of CAR-T therapy are considered investigational. |

Note:  

c Relapsed or refractory disease is defined as progression after 2 or more lines of systemic therapy (which may or may not include therapy supported by autologous cell transplant).
Documentation Requirements

The patient’s medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

For Kymriah™ (tisagenlecleucel) for relapsed or refractory patients and ALL of the following:

- Confirmed diagnosis of B-cell acute lymphoblastic leukemia with CD19 tumor expression
- 25 years of age or younger at the time of infusion
- Have not received prior treatment with tisagenlecleucel or any other gene therapy, nor is being considered for treatment with any other gene therapy
- Have adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis (collection of blood)
- Do not have any of the following:
  - Burkitt lymphoma
  - Active hepatitis B, C, or any uncontrolled infection
  - Grade 2 to 4 graft-versus-host disease
  - The presence of a genetic syndrome, with the exception of Down syndrome
  - Received cellular therapy from a donor, such as donor lymphocyte infusion, within 6 weeks prior to tisagenlecleucel infusion
  - Patient has active central nervous system 3 acute lymphoblastic leukemia (ie, white blood cell count 5 or greater cells/μL in cerebrospinal fluid with presence of lymphoblasts)

For Yescarta™ (axicabtagene ciloleucel) and Kymriah™ (tisagenlecleucel) necessary for relapsed or refractory patients and ALL of the following:

- Adults (age 18 or older) at the time of infusion
- Tissue tests confirm the diagnosis of one of the following:
  - 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
- Have received adequate prior therapy
- Have adequate organ and bone marrow function as determined by the treating oncologist/hematologist
- Have not received prior CD19-directed CAR T-cell therapy treatment or any other gene therapy, nor is being considered for treatment with any other gene therapy
- Do not have primary central nervous system lymphoma
### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td><strong>CPT</strong></td>
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</tr>
<tr>
<td>36511</td>
<td>Therapeutic apheresis; for white blood cells</td>
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<tr>
<td><strong>HCPCS</strong></td>
<td></td>
</tr>
<tr>
<td>Q2041</td>
<td>Axicabtagene ciloleucel (Yescarta™), up to 200 million autologous anti-CD19 car positive viable T cells, including leukapheresis and dose preparation procedures, per therapeutic dose</td>
</tr>
<tr>
<td>Q2042</td>
<td>Tisagenlecleucel (Kymriah™), up to 600 million CAR-positive viable T cells, including leukapheresis and dose preparation procedures, per therapeutic dose</td>
</tr>
<tr>
<td>S2107</td>
<td>Adoptive immunotherapy ie, development of specific antitumor reactivity (eg, tumor-infiltrating lymphocyte therapy) per course of treatment</td>
</tr>
<tr>
<td><strong>Non-Covered</strong></td>
<td>These codes are not separately reimbursable</td>
</tr>
<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>
</tr>
<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>
</tr>
<tr>
<td>0539T</td>
<td>Chimeric antigen receptor T-cell (CAR-T) therapy; receipt and preparation of CAR-T cells for administration</td>
</tr>
<tr>
<td>0540T</td>
<td>Chimeric antigen receptor T-cell (CAR-T) therapy; CAR-T cell administration, autologous</td>
</tr>
</tbody>
</table>

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

### Related Information

Autologous lymphocytes used as part of adoptive immunotherapy may be harvested in apheresis procedure or may be isolated from resected tumor tissue.

The recommended dosage of tisagenlecleucel for patients with B-cell acute lymphoblastic leukemia who are 50 kg or less is $0.2$ to $5.0 \times 10^6$ chimeric antigen receptor–positive viable T cells.
per kilogram of body weight intravenously; for patients above 50 kg, dose is 0.1 to 2.5×10^8 total chimeric antigen receptor–positive viable T cells (non-weight-based) intravenously.

The recommended target dose of tisagenlecleucel for patients with large B-cell lymphoma is 0.6 to 6.0 × 10^8 chimeric antigen receptor–positive viable T cells intravenously.

The recommended target dose of axicabtagene ciloleucel for patients with large B-cell lymphoma is 2×10^6 CAR-positive viable T cells per kg body weight, with a maximum of 2×10^8 chimeric antigen receptor–positive viable T cells intravenously.

Central nervous system (CNS) disease for B-cell acute lymphoblastic leukemia is defined by the following groups:

- **CNS 1:** Absence of blasts on cerebrospinal fluid cytospin preparation, regardless of the white blood cell (WBC) count
- **CNS 2:** WBC count of less than 5/mL and blasts on cytospin findings
- **CNS 3:** WBC count of 5/mL or more and blasts on cytospin findings and/or clinical signs of CNS leukemia (eg, facial nerve palsy, brain/eye involvement, hypothalamic syndrome)

Tisagenlecleucel and axicabtagene ciloleucel have black box warnings because of the risks of cytokine release syndrome and neurologic toxicities that include fatal or life-threatening reactions. They should not be administered to patients with active infection or inflammatory disorders. It is recommended that severe or life-threatening cytokine release syndrome be treated with tocilizumab. Patients should be monitored for neurologic events after treatment.

Tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta) are available only through a restricted program under a risk evaluation and mitigation strategy (REMS) called the Kymriah REMS and Yescarta REMS, respectively. The requirement for the REMS components are as follows:

- **Health care facilities** that dispense and administer tisagenlecleucel or axicabtagene ciloleucel must be enrolled and comply with the REMS requirements.
- **Certified health care facilities** must have onsite, immediate access to tocilizumab, and ensure that a minimum of 2 doses of tocilizumab are available for each patient for administration within 2 hours after tisagenlecleucel or axicabtagene ciloleucel infusion, if needed for treatment of cytokine release syndrome.
Certified health care facilities must ensure that health care providers who prescribe, dispense, or administer tisagenlecleucel or axicabtagene ciloleucel are trained to manage cytokine release syndrome and neurologic toxicities.

**Consideration of Age**

The ages noted in the policy statements are based on the FDA labeling for these agents.

**Evidence Review**

**Description**

The spontaneous regression of certain cancers (eg, renal cell carcinoma, melanoma) supports the idea that a patient’s immune system can delay tumor progression and, on rare occasions, can eliminate tumors altogether. These observations have led to research into various immunotherapies designed to stimulate a patient’s own immune system. Chimeric antigen receptor T-cell therapy is a specific form of adoptive immunotherapy that involves harvesting cells from a patient or donor, a manufacturing process during which cells are genetically modified with engineered CAR protein to permit targeted activation and therapy, and infusion of cells into the patient.

**Background**

**Acute Lymphoblastic Leukemia (ALL)**

B-cell ALL is a malignancy (clonal) of the bone marrow in which the early lymphoid precursors of the white blood cells (called lymphoblasts) proliferate and replace the normal hematopoietic cells of the marrow. This results in overcrowding of the bone marrow, as well as the peripheral organs (particularly the liver, spleen, and lymph nodes) by the lymphoblasts. As a consequence, the leukemic blasts displace the normal hematopoietic bone marrow and cause cytopenias in all three cell lineages (anemia, thrombocytopenia, granulocytopenia). Leukostasis affecting brain and lung may also occur. Death occurs commonly due to severe pancytopenia and resulting infections. Refractory (resistant) disease is defined as those patients who fail to obtain a
complete response with induction therapy, ie, 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). Relapsed disease describes the reappearance of leukemia cells in the bone marrow or peripheral blood after the attainment of complete remission. Minimal residual disease (MRD) refers to the presence of disease in cases deemed to be in complete remission by conventional pathologic analysis. MRD positivity is defined as the presence of 0.01% or more ALL cells and has been shown to be a strongest prognostic factor to predict the risk of relapse and death when measured during and after induction therapy in both newly diagnosed and relapsed ALL. In a meta-analysis of 20 studies of 11249 pediatric ALL, Berry et al (2017) reported a hazard ratio for event-free survival in MRD-negative patients compared with MRD-positive patients of 0.23 (95% confidence interval, 0.18 to 0.28). \(^1\)

Approximately 5000 cases of B-cell ALL are diagnosed every year in the United States, \(^2\) and approximately 620 pediatric and young adult patients with B-cell ALL will relapse each year in the United States. \(^3\) B-cell ALL is largely a disease of the young, with approximately 60% of cases occurring in patients younger than 20 years old with a median age at diagnosis of 15 years. \(^2\)

**Treatment**

While treatable in 85% cases, approximately 15% of children and young adults with ALL will relapse and 2% to 3% of ALL patients are primary refractory. \(^4\) Retreatment of refractory or relapsed ALL is generally unsuccessful and associated with a high mortality rate. \(^5\) The 2-year survival rate among patients with ALL who relapse after hematopoietic cell transplantation is 15%. \(^6\) The Food and Drug Administration (FDA) approved clofarabine (as a single agent or in combination) in 2004 and blinatumomab in 2014 for relapsed and refractory ALL. Reported median objective response rates in the pivotal trials of the 2 agents were 19.7% and 33%, the median durations of response were 2.5 months and 6 months, and median overall survival durations were 3 months and 7.5 months, respectively. \(^7,\) \(^8\) Note that the percentages of patients treated with 3 or more prior treatments of clofarabine and blinatumomab trial were 62% and 7%, respectively. Nevertheless, treatment options for patients with relapsed or refractory ALL are limited, associated with poor outcomes and high toxicity and the disease remains incurable.

**Diffuse Large B Cell Lymphoma (DLBCL)**

DLBCL is the most common histologic subtype of non-Hodgkin lymphoma and accounts for approximately 25% of non-Hodgkin lymphoma cases. \(^9\) DLBCL exhibits large heterogeneity in
morphologic, genetic, and clinical aspects and multiple clinicopathologic entities are defined by the 2016 World Health Organization classification, which are sufficiently distinct to be considered separate diagnostic categories. Teras et al (2016) has estimated that 27650 new cases of DLBCL were diagnosed in the United States in 2016.¹⁰

**Treatment**

Treatment in the first-line setting (particularly rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) is associated with a 5-year survival rate ranging from 60% to 70%.¹¹ However, based on a number of prognostic factors, 20% to 50% of DLBCL cases are refractory or relapse after first-line chemotherapy.¹²,¹³ The response to subsequent salvage chemotherapy and consolidation with autologous cell transplantation is suboptimal. A retrospective analysis of the SCHOLAR-1 study by Crump et al (2017), which pooled data from 2, phase 3 clinical trials and 2 observational cohorts, included 636 patients with refractory DLBCL.¹⁴ The objective response rate to the next line of therapy was 26%, with 7% achieving a complete response. Median overall survival was 6.3 months and 2-year survival 20%. Refractory DLBCL was defined as progressive disease or stable disease as best response at any point during chemotherapy (>4 cycles of first-line or 2 cycles of later-line therapy) or as relapse 12 or fewer months after autologous cell transplantation.

**Adoptive Immunotherapy**

Adoptive immunotherapy uses “activated” lymphocytes as a treatment modality. Both nonspecific and specific lymphocyte activation are used therapeutically. The nonspecific, polyclonal proliferation of lymphocytes by cytokines (immune system growth factors), also called autolymphocyte therapy, increases the number of activated lymphocytes.

Initially, this treatment was performed by harvesting peripheral lymphokine-activated killer cells and activating them ex vivo with the T-cell growth factor interleukin-2 (IL-2) and other cytokines. More recent techniques have yielded select populations of cytotoxic T lymphocytes with specific reactivity to tumor antigens. Peripheral lymphocytes are propagated in vitro with antigen-presenting dendritic cells (DC) that have been pulsed with tumor antigens. Alternatively, innate tumor-infiltrating lymphocytes (TIL) from the tumor biopsy are propagated in vitro with IL-2 and anti-CD3 antibody, a T-cell activator. Expansion of TIL for clinical use is labor intensive and requires laboratory expertise. Only a few cancers are infiltrated by T cells in significant numbers; of these, TIL can be expanded in only approximately 50% of cases.¹⁵
**Adoptive Cell Transfer**

The major research challenge in adoptive immunotherapy is to develop immune cells with antitumor reactivity in quantities sufficient for transfer to tumor-bearing patients.

Adoptive cellular therapy is “the administration of a patient’s own (autologous) or donor (allogeneic) antitumor lymphocytes following a lymphodepleting preparative regimen.” Protocols vary, but include these common steps:

1. lymphocyte harvesting (either from peripheral blood, tumor biopsy, or donor blood)
2. propagation of tumor-specific lymphocytes in vitro using various immune modulators
3. selection of lymphocytes with reactivity to tumor antigens and/or modification of lymphocytes to bear tumor-antigen targeted receptors
4. lymphodepletion of the host with immunosuppressive agents
5. adoptive transfer (ie, transfusion) of lymphocytes back into the tumor-bearing host.

In an attempt to regulate the host immune system further, recent protocols have used various cytokines (eg, IL-7 and IL-15 instead of IL-2) to propagate lymphocytes. Protocols also differ in the extent of host lymphodepletion induced prior to transfusing lymphocytes to the tumor-bearing host.

Allogeneic stem cell transplantation following nonmyeloablative conditioning of the recipient (ie, reduced-intensity conditioning) may also be referred to as “adoptive immunotherapy” in the literature. However, reduced-intensity conditioning cell transplantation relies on a donor-vs-malignancy effect of donor lymphocytes. In contrast, the adoptive immunotherapy techniques described in this evidence review enhance autoimmune effects primarily. The use of reduced-intensity conditioning in cell transplantation is discussed for specific cancers in individual policies related to stem cell transplantation.

**Chimeric Antigen Receptor T Cell Therapy**

Due to difficulties in expanding innate TILs, genetic modification techniques have been harnessed to decorate propagated T cells with engineered chimeric antigen receptors (CARs) that are composed of several functional components: a tumor antigen-targeting single chain variable fragment (scVF) (eg, anti-CD19), a hinge region, a T-cell activation domain (eg, CD3),
and one or more costimulatory domains (eg, CD28, 4-1 BB). Viral vector genetic modification approaches (eg, retroviral, lentiviral) have traditionally been used to transfet T cells with CAR genes.¹⁷

**Tisagenlecleucel**

Tisagenlecleucel is adoptive immunotherapy in which the T-cells of a patient are modified by genetic engineering using a lentiviral vector. The resulting genetic modified cells express a CD-19-directed chimeric antigen receptor protein that consists of an extracellular portion that has a murine anti-CD19 single-chain antibody fragment as well as an intracellular portion that contains T-cell signaling and co-stimulatory domains. Once injected, the genetically modified T-cells selectively target and bind to CD19 antigen expressed on the surface of B cells and tumors derived from B cells. Subsequently, the intracellular signaling domains play crucial roles in T-cell activation, persistence, and effector functions.¹⁸

**Axicabtagene Ciloleucel**

Similar to tisagenlecleucel, axicabtagene ciloleucel is adoptive immunotherapy in which the T-cells of a patient are modified genetically using a retroviral vector. The resulting genetically modified cells express a CD-19-directed chimeric antigen receptor protein that has a murine single-chain variable fragment with specificity for CD19. Once injected, the genetically modified T-cells selectively target and bind to CD19 antigen expressed on the surface of normal and malignant B cells.¹⁹

**Summary of Evidence**

**Tisagenlecleucel**

For individuals who are up to 25 years of age with relapsed or refractory B-cell ALL who receive tisagenlecleucel, the evidence includes multiple single-arm prospective trials. The relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The pivotal single-arm trials reported an 81% response rate (measured by complete response or complete remission with incomplete blood count) in heavily pretreated patients. All patients who achieved a CR or CRi were also minimal residual disease-negative, which is predictive of survival in ALL patients. After a median follow-up of 13.1 months, the median duration of response was not
reached. The observed benefits seen with tisagenlecleucel were offset by a high frequency and severity of adverse events. The CRS was observed in more than half (77%) of the patients, and approximately 88% had an adverse event at grade 3 or higher. Long-term follow-up, real-world evidence, and post-marketing studies are required to assess the generalizability of tisagenlecleucel efficacy and safety outside of the clinical trial setting. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are adults with a histologically confirmed diagnosis of aggressive NHL (eg, DLBCL not otherwise specified, high-grade B-cell lymphoma, transformed follicular lymphoma) who receive tisagenlecleucel, the evidence includes a single-arm prospective trial. The relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The pivotal single-arm trial reported a 52% overall response rate (measured by complete or partial remission) in heavily pretreated patients. After a median follow-up of 14 months, the median duration of response was not reached. The observed benefits were offset by a high frequency and severity of adverse events. Any grade CRS was observed in 58% of the patients, and 63% had an adverse event at grade 3 or higher. Long-term follow-up and real-world evidence are required to assess the generalizability of tisagenlecleucel efficacy and safety outside of the clinical trial setting. The manufacturer has agreed to a postmarketing requirement observational registry study to collect safety information for patients treated with the marketed product. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Axicabtagene Ciloleucel**

For individuals who are adults with a histologically confirmed diagnosis of aggressive NHL (eg, DLBCL not otherwise specified, high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, transformed follicular lymphoma) who receive axicabtagene ciloleucel, the evidence includes a single-arm prospective trial. The relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The pivotal single-arm trial reported a 83% overall response rate (measured by complete or partial remission) in heavily pretreated patients. After a median follow-up of 27.1 months, the median duration of response was 11.1 months. The observed benefits were offset by a high frequency and severity of adverse events. CRS was observed in more than half of the patients, and 98% had an adverse event at grade 3 or higher. Long-term follow-up and real-world evidence are required to assess the generalizability of axicabtagene ciloleucel efficacy and safety outside of the clinical trial setting. The manufacturer has agreed to a postmarketing requirement observational registry study to collect safety information for
patients treated with the marketed product. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 1.

**Table 1. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Tisagenlecleucel</strong></td>
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<tr>
<td>NCT02445248a</td>
<td>A Phase II, Single Arm, Multicenter Trial to Determine the Efficacy and Safety of CTL019 in Adult Patients With Relapsed or Refractory Diffuse Large B-cell Lymphoma</td>
<td>116</td>
<td>Feb 2023</td>
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<tr>
<td>NCT02445222a</td>
<td>Long Term Follow-Up of Patients Exposed to Lentiviral-Based CD19 Directed CAR T-Cell Therapy</td>
<td>620</td>
<td>May 2035</td>
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<tr>
<td>NCT03876769a</td>
<td>A Phase II Trial of Tisagenlecleucel in First-Line High-Risk (HR) Pediatric and Young Adult Patients with B-cell Acute Lymphoblastic Leukemia (B-ALL) Who Are Minimal Residual Disease Positive at the End of Consolidation Therapy</td>
<td>140</td>
<td>Aug 2027</td>
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<tr>
<td><strong>Axicabtagene ciloleucel</strong></td>
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<tr>
<td>NCT02601313a</td>
<td>A Phase 2 Multicenter Study Evaluating Subjects with Relapse/Refractory Mantle Cell Lymphoma (ZUMA-2)</td>
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<td>Jan 2035</td>
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<tr>
<td>NCT02614066a</td>
<td>A Study Evaluating KTE-C19 in Adult Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (r/r ALL) (ZUMA-3) (ZUMA-3)</td>
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<td>Mar 2034</td>
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<tr>
<td>NCT02625480a</td>
<td>A Multi-Center Study Evaluating KTE-C19 in Pediatric and Adolescent Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ZUMA-4)</td>
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<tr>
<td>NCT03105336a</td>
<td>A Phase 2 Multicenter Study of Axicabtagene Ciloleucel in Subjects With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma (ZUMA-5)</td>
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<tr>
<td><strong>Unpublished</strong></td>
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<td></td>
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<tr>
<td>NCT No.</td>
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<td>Completion Date</td>
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<tr>
<td>NCT02228096*</td>
<td>A Phase II, Single Arm, Multicenter Trial to Determine the Efficacy and Safety of CTL019 in Pediatric Patients With Relapsed and Refractory B-cell Acute Lymphoblastic Leukemia</td>
<td>64</td>
<td>May 2019</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
* Denotes industry-sponsored or cosponsored trial.

Practice Guidelines and Position Statements

**National Comprehensive Cancer Network**

Current guidelines from the National Comprehensive Cancer Network do not include recommendations for chimeric antigen receptor T-cell therapy in certain hematologic cancers, including the central nervous system (eg, secondary CNS lymphoma) and Hodgkin lymphoma.

Current NCCN guidelines for acute lymphoblastic leukemia (v.1.2020) recommend (category 2A) tisagenlecleucel as a treatment option for:

- Philadelphia chromosome-positive patients 26 years or less in age with refractory disease or 2 or more relapses and failure of 2 tyrosine kinase inhibitors.
- Philadelphia chromosome-negative patients 26 years or less in age with refractory disease or 2 or more relapses.

Current Network guidelines for B-cell non-Hodgkin lymphoma (v.4.2019) recommend (category 2A) axicabtagene ciloleucel or tisagenlecleucel as a treatment option for:

- For histological transformation to diffuse large B-cell lymphoma after multiple lines of prior therapies which include ≥2 chemo-immunotherapy regimens for the indolent or transformed disease.
- For relapsed or refractory disease diffuse large B-cell lymphoma after multiple lines of prior therapies which include ≥2 chemo-immunotherapy regimens for the indolent or transformed disease.

**Note:** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Pediatric Acute Lymphoblastic Leukemia V.1.2020 and B-Cell Lymphomas V.4.2019. © National Comprehensive
Medicare National Coverage

The Centers for Medicare & Medicaid Services (CMS) has published a Proposed Decision Memo regarding the use of chimeric antigen receptor (CAR) T-cell therapy for the treatment of cancer. CMS proposes to cover autologous treatment with T-cells expressing at least one CAR through coverage with evidence development when prescribed by a treating oncologist, performed in a hospital, and when all of the following requirements are met:

- Patient has:
  - relapsed or refractory cancer; and
  - is not currently experiencing any comorbidity that would otherwise preclude benefit.

- The hospital has:
  - a Cellular Therapy Program consisting of an integrated medical team; and
  - a designated care area; and
  - written guidelines for the administration of chimeric antigen receptor T-cell therapy for patient communication, monitoring, and transfer to an intensive care unit.

- The treatment meets the criteria in section a or b, below:
  - a) The treatment is an FDA-approved biological, indicated for use in a hospital setting.
  - b) The treatment is an FDA-approved biological, indicated for use identified in the National Comprehensive Cancer Network Drugs and Biologics Compendium.

CMS proposes to non-cover the use of CAR-expressing T-cells for any treatment that does not involve an FDA-approved biological product.
Regulatory Status

On August 30, 2017, tisagenlecleucel (Kymriah™; Novartis) was approved by the FDA for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse.

On May 1, 2018, tisagenlecleucel (Kymriah™; Novartis) was approved by the FDA for the treatment of adults with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy including DLBCL not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

On October 18, 2017, axicabtagene ciloleucel (Yescarta™; Kite Pharma) was approved by the FDA for the treatment of adults with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

References


History

<table>
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<tr>
<th>Date</th>
<th>Comments</th>
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<tbody>
<tr>
<td>07/01/20</td>
<td>New policy, approved June 9, 2020, created with literature review through July 2019.</td>
</tr>
<tr>
<td></td>
<td>Add to Therapy section. FDA-approved tisagenlecleucel and axicabtagene cilioleucel therapies were moved from policy 8.01.01 Adoptive Immunotherapy to create this new standalone policy 8.01.63.</td>
</tr>
</tbody>
</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2020 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination Is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:
Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)


Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost.

Call 800-722-1471 (TTY: 800-842-5357).

Oromo (Cushite):

Lakkoofsa bibiliaa 800-722-1471 (TTY: 800-842-5357) ti bibiliaa.

French (French):

Appelez le 800-722-1471 (TTY: 800-842-5357).

Kreyòl ayisyen (Creole):

Deutsche (German):

Hmoob (Hmong):
Tsab ntawv tshaj xo no muaj cov ntsiab lus tseeem ceeb. Tej zaum tsab ntawv tshaj xo no muaj cov ntsiab lus tseeem ceeb bong kaj daim ntawv thov kaj kaj thaj kaj yuav tau uu ghi yuav tau uu wp sabotage kaj kaj uu bong kaj uu bong kaj kaj yuav tau uu baaj kaj kaj yuav tau uu baaj kaj kaj yuav tau uu baaj kaj kaj yuav tau uu baaj kaj kaj yuav tau uu baaj kaj yuav tau uu baaj kaj kaj yuav tau uu baaj kaj kaj yuav tau uu baaj kaj kaj yuav tau uu baaj.

Iloko (Ilocano):
Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaar mabalin nga adda ket naglaon iti Napateg nga impormasion maipangep ii aplikayson lnong coverage babaen iti Premera Blue Cross. Daytoy ket mabalin dagiti importante a pelsa iti daytoy a pakdaar. Mabalin nga adda rumbeng nga aramendyo nga adda sangkay dagiti partikular a naituding nga napateg ngi pagsasao nga awan ti bayadanyo. Tumawag ti numero nga osa 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):
Questo avviso contiene informazioni importanti. Questo avviso può contenere informazioni importanti sulla tua domanda o copertura attraverso Premera Blue Cross. Potrebbero esserci date chiave in questo avviso. Potrebbe essere necessario un tuo intervento entro una scadenza determinata per consentirti di mantenere la tua copertura o sovvenzione. Hai il diritto di ottenere queste informazioni e assistenza nella tua lingua gratuitamente.

Chiama 800-722-1471 (TTY: 800-842-5357).

中文 (Chinese):
本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知內可能有重要日期。您可能需要在截止日期之前採取行動。以保留您的健康保險或費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357).
Japanese (Japanese):
この通知には重要な情報が含まれています。この通知には、Premera Blue Crossの申請または補償範囲に関する重要な情報が含まれています。この通知には、記載されている可能性がある重要な日付をご確認ください。健康保険や無料サポートを維持するには、期限の日までに行動を取らなければなりません。ご希望の言語による情報とサポートが無料で提供されます。800-722-1471 (TTY: 800-842-5357)までお電話ください。

한국어 (Korean):
본 통지서에는 중요한 정보가 들어 있습니다. 즉 이 통지서는 귀하의 신청에 관하여 그리고 Premera Blue Cross를 통한 커버리지에 관한 정보를 포함하고 있을 수 있습니다. 귀하는 귀하의 건강 커버리지를 계속 유지하거나 비용을 절감하기 위해서 일정한 마감일까지 조치를 취해야 할 필요가 있을 수 있습니다. 귀하의 이러한 정보와 도움은 귀하의 안의 비용 부담없이 얻을 수 있는 권리가 있습니다. 800-722-1471 (TTY: 800-842-5357)로 전화하십시오.

Română (Romanian):

Русский (Russian):
Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Español (Spanish):
Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Tagalog (Tagalog):
Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon. Ang paunawa na ito ay maaring magalang ng mahalagang impormasyon tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng Premera Blue Cross. Maaaring may mga mahalagang petsa dito sa paunawa. Maaring may fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

ไทย (Thai):
ประกาศนี้ยังมีข้อมูลที่สำคัญ การขอและการชดเชยเป้าหมายของประกันสุขภาพของคุณ Premera Blue Cross และการมีส่วนร่วมในการดูแลสุขภาพของคุณ คุณควรตรวจสอบข้อมูลในประกาศนี้ให้แน่ใจว่าจะสามารถเข้าถึงข้อมูลของประกันสุขภาพของคุณได้ ยินดีให้คุณใช้สิทธิ์ฟรีและข้อมูลที่มีอยู่ในประกาศนี้ โปรดติดต่อ 800-722-1471 (TTY: 800-842-5357)

Polski (Polish):
To ogłoszenie może zawierać ważne informacje. To ogłoszenie może zawierać ważne informacje odnośnie Polskiej wniosku lub zakresu świadczeń poprzez Premera Blue Cross. Prosimy zwrócić uwagę na kluczowe daty, które mogą być zawarte w tym ogłoszeniu aby nie przekroczyć terminów w przypadku utraty polisy ubezpieczeniowej lub pomocy związanej z kosztami. Macie prawo do bezpłatnej informacji we własnym języku. Zadzwoń pod 800-722-1471 (TTY: 800-842-5357).

Português (Portuguese):
Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir datas importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde ou ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

Tiếng Việt (Vietnamese):