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 In this technique, certain types of immune system cells are withdrawn from the person to be treated.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 three adoptive immunotherapy treatments, Kymriah™ (tisagenlecleucel), Tecartus™ (brexucabtagene autoleucel), 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>
</table>
| Kymriah™ (tisagenlecleucel) IV | **Kymriah™ (tisagenlecleucel) is considered medically necessary for relapsed\(^a\) or refractory\(^b\) patients with B-cell acute lymphoblastic leukemia if they meet all of the following criteria:**  
  - Confirmed diagnosis of CD19-positive B-cell acute lymphoblastic leukemia with morphologic bone marrow tumor involvement (≥5% lymphoblasts)  
  - Are up to 25 years old at the time of infusion  
  - Have not received prior treatment with tisagenlecleucel or any other gene therapy or are 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  
  - 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  
    - Concomitant genetic syndrome with the exception of Down syndrome  
    - Received allogeneic cellular therapy, such as donor lymphocyte infusion, within 6 weeks prior to tisagenlecleucel infusion  
    - Active central nervous system 3 (see Related Information) acute lymphoblastic leukemia (ie, white blood cell count ≥5 cells/μL in cerebrospinal fluid with presence of lymphoblasts). |

**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...
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| Kymria™ (tisagenlecleucel) IV                  | Kymria™ (tisagenlecleucel) is considered medically necessary for relapsed or refractory<sup>c</sup> patients with aggressive types of non-Hodgkin lymphoma 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; 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  

**Note:**  
Tisagenlecleucel intravenous infusion is considered investigational for the treatment of relapsed or refractory primary mediastinal large B-cell lymphoma.  

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).

| Yescarta™ (axicabtagene ciloleucel) IV         | Yescarta™ (axicabtagene ciloleucel) is considered medically necessary for relapsed or refractory<sup>c</sup> patients with aggressive types of non-Hodgkin lymphoma if they meet all of the following criteria: |
## Treatment

<table>
<thead>
<tr>
<th>Medical Necessity</th>
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</thead>
<tbody>
<tr>
<td>Are adults (age ≥18) at the time of infusion</td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td>Received adequate prior therapy including all of the following:</td>
</tr>
<tr>
<td>- Anti-CD20 monoclonal antibody for CD20-positive tumor</td>
</tr>
<tr>
<td>- Anthracycline-containing chemotherapy regimen</td>
</tr>
<tr>
<td>- For subjects with transformed follicular lymphoma, prior chemotherapy for follicular lymphoma and subsequently have chemorefractory disease after transformation to diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td>Have adequate organ and bone marrow function as determined by the treating oncologist/hematologist</td>
</tr>
<tr>
<td>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</td>
</tr>
</tbody>
</table>

**AND**

<table>
<thead>
<tr>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not have primary central nervous system lymphoma</td>
</tr>
</tbody>
</table>

**Note:** 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).

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### Tecartus™ (brexucabtagene autoleucel) IV

Tecartus™ (brexucabtagene autoleucel) is considered medically necessary for relapsed or refractory patients with mantle cell lymphoma if they meet all of the following criteria:

- Are adults (age ≥18) at the time of infusion
- Histologically confirmed diagnosis of mantle cell lymphoma
- Received adequate prior therapy including anthracycline- or bendamustine-containing chemotherapy, anti-CD20 antibody, and a Bruton tyrosine kinase inhibitor (example ibritinib or acalabrutinib)
- 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
## Treatment | Medical Necessity
--- | ---

### Note:
- Relapsed or refractory disease is defined as disease progression after last regimen or failure to achieve a partial remission or complete remission to the last regimen.

## Treatment | Investigational
--- | ---

**Other applications**

Other applications of CAR-T therapy are considered investigational.

## 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
  - 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) 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
# Documentation Requirements

- 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

For **Tecartus™ (brexucabtagene autoleucel)** for relapsed or refractory patients and **ALL of the following:**
- Are adults (age ≥18) at the time of infusion
- Histologically confirmed diagnosis of mantle cell lymphoma
- 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 or are being considered for treatment with any other gene therapy

## Coding

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<tr>
<td>36511</td>
<td>Therapeutic apheresis; for white blood cells</td>
</tr>
<tr>
<td>HCPCS</td>
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<tr>
<td>C9073</td>
<td>brexucabtagene autoleucel, up to 200 million autologous anti-cd19 car positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose ([Tecartus™]) (new code effective 1/1/21)</td>
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<td>J3590</td>
<td>Unclassified biologics (Tecartus™)</td>
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<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>
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<tr>
<td>Code</td>
<td>Description</td>
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<tr>
<td>-------</td>
<td>-----------------------------------------------------------------------------</td>
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<tr>
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<td>Tisagenlecleucel (Kymriah™), up to 600 million car-positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose</td>
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<td>S2107</td>
<td>Adoptive immunotherapy ie, development of specific antitumor reactivity (eg, tumor-infiltrating lymphocyte therapy) per course of treatment</td>
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</table>

**Non-Covered**

These codes are not separately reimbursable

<table>
<thead>
<tr>
<th>Code</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>
</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 (Kymriah) for patients with B-cell acute lymphoblastic leukemia who are 50 kg or less is 0.2 to 5.0×10⁶ chimeric antigen receptor–positive viable T cells per kilogram of body weight intravenously; for patients above 50 kg, dose is 0.1 to 2.5×10⁸ total chimeric antigen receptor–positive viable T cells (non-weight-based) intravenously.

The recommended target dose of tisagenlecleucel (Kymriah) for patients with large B-cell lymphoma is 0.6 to 6.0 × 10⁸ chimeric antigen receptor–positive viable T cells intravenously.

The recommended target dose of axicabtagene ciloleucel (Yescarta) for patients with large B-cell lymphoma is 2×10⁶ CAR-positive viable T cells per kg body weight, with a maximum of 2×10⁸ chimeric antigen receptor– positive viable T cells intravenously.
The recommended target dose of brexucabtagene autoleucel (Tecartus) for patients with mantle cell lymphoma is $2 \times 10^6$ CAR-positive viable T cells per kg body weight, with a maximum of $2 \times 10^8$ 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 (Kymriah), axicabtagene ciloleucel (Yescarta), and brexucabtagene autoleucel (Tecartus) 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), and brexucabtagene autoleucel (Tecartus) are available only through a restricted program under a risk evaluation and mitigation strategy (REMS) called the Kymriah REMS and Yescarta REMS, respectively. The requirements for the REMS components are as follows:

- Health care facilities that dispense and administer these CAR T therapies 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 of these CAR T, if needed for treatment of cytokine release syndrome.
- Certified health care facilities must ensure that health care providers who prescribe, dispense, or administer these CAR T therapies 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**

Chimeric antigen receptor (CAR) T cells are genetically engineered cells that represent a novel class of cancer immunotherapy. In general, the process of autologous CAR T-cell therapy begins with harvesting white blood cells from the patient via leukapheresis followed by T-cell receptor activation and genetic engineering via retroviral or lentiviral transduction. After the CAR T cells are generated, they are expanded to clinically relevant numbers, undergo quality control testing, and are cryopreserved. Commercial CAR T-cell products are manufactured at a centralized facility, necessitating transfer of the apheresis product to the manufacturing site, and the final cryopreserved CAR T-cell product back to the treatment facility. Typically, the patient undergoes lymphodepleting chemotherapy to create a favorable immune environment for CAR T-cell activity prior to receiving a single intravenous infusion of the product. Three commercial CAR T cell products have been approved by the U.S. Food and Drug Administration for the treatment of cancer. Tisagenlecleucel (Kymriah) is approved for treatment of subsets of patients with leukemia and lymphoma and axicabtagene ciloleucel (Yecarta) and brexucabtagene autoleucel (Tecartus) are approved to treat subsets of patients with lymphoma.

**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. The incidence of DLBCL is approximately 7 cases per 100,000 persons per year.\textsuperscript{10}

**Treatment**

Treatment in the first-line setting include multiple chemotherapy and/or immunotherapy options that typically include rituximab. While majority of patients responds well to first-line immunochemotherapy combinations containing rituximab, 10 to 15\% have primary refractory disease within 3 months after treatment initiation and and another 20 to 35\% have a relapse.\textsuperscript{11} Of those who relapse or are refractory, 40 to 60\% of patients may respond to second-line chemotherapy. Treatment of relapsed/refractory cases is generally stratified according to hematopoietic cell transplant eligibility. There is general consensus that salvage therapy followed by autologous transplantation is the preferred treatment for medically eligible patients with a first relapse of DLBCL or primary refractory DLBCL. Approximately 50\% of patients who relapse or are refractory to first line agents proceed to undergo autologous hematopoietic stem-cell transplantation, and of these, approximately 30 to 40\% remain progression-free 3 years after transplantation.\textsuperscript{12,13,14,15,16} Patients who are ineligible for as second-line therapy that includes high-dose chemotherapy and hematopoietic stem-cell transplantation, prognosis is often poor with a median overall survival of 4.4 months. Overall survival at 1 year is 23\% and 16\% at year 2.\textsuperscript{16} Patients who relapse after autologous transplantation, options are limited that includes allogeneic hematopoietic stem-cell transplantation. However, the procedure can only be performed if patient is chemo-responsive and a donor is available. Further the procedure is associated with a high risk of complications. Mortality risk unrelated to disease relapse is 23\% at 1 year.\textsuperscript{17,18,19} FDA has also approved agents for refractory/relapsed DLBCL include pembrolizumab (Keytruda), polutuzumab vedotin-piiq (Polivy), selinexor (Xpovio) and tafasitamab-cxix (Monjuvi).

**Mantle Cell Lymphoma (MCL)**

MCL is a rare B-cell malignancy classified as an aggressive form of non-Hodgkin lymphoma that arises from cells originating in the “mantle zone” of the lymph node and typically affects men over the age of 60. It accounts for approximately 3-6\% of all non-Hodgkin lymphoma in the United States and differs from diffuse large B cell lymphoma (another subtype of non-Hodgkin lymphoma).\textsuperscript{20,21,22} In 2018, the overall incidence of MCL in the U.S was 3,500 with 5-year and 10-year prevalence of 12,000 and 18,000 cases. Median age at the time of diagnosis is 68, a
majority of patients are non-Hispanic white males and more than 70% of patients present with stage IV disease. The majority (75%) of cases initially present with lymphadenopathy while presentation is extranodal in the remaining 25 percent. In most cases of MCL, chromosomal translocation results in aberrant expression of cyclin D1, leading to cell cycle dysregulation. Many signaling pathways are constitutively activated and/or deregulated in MCL, including the B-cell receptor signaling pathway.

**Treatment**

There is no standard of care that exists for second-line and higher chemotherapy when a patient has relapsed or refractory MCL. Second line therapies typically depend on the front line therapy utilized, comorbidities, the tumor’s sensitivity to chemotherapy, and overall risk-benefit. Potential salvage regimens include ibrutinib, acalabrutinib, lenalidomide, combination chemotherapy, bortezomib, temsirolimus.

Despite availability of multiple treatments, MCL is not curable (with the possible exception of hematopoietic cell transplantation). Median overall survival in modern trials incorporating intensive therapy is 8 to 10 years with no plateau in the survival curve. Shorter survival times are seen with less intensive therapy. Multiple prognostic indices are used in MCL patients to guide course of treatment. First-line treatment of MCL can consist of aggressive therapy or less-aggressive therapy, depending on patient status at baseline. It generally consists of chemotherapy in combination with rituximab. Only 30 to 40% of patients have a durable long-term remission after chemo immunotherapy first line therapy. Progression is common, with a median time to treatment failure of less than 18 months. Virtually all patients will have refractory or recurrent disease. Treatment of recurrent MCL is difficult, due to the rapid development of chemotherapy resistance. There are multiple preferred chemotherapy regimens that may be offered and choice is primarily made based on prior treatment history, patient comorbidities, and performance status. The expected toxicities of a given regimen as well as clinician’s experience with the regimens are additional considerations. A preferred order for their use has not been established. Most of these regimens have not been compared directly in randomized trials. Given the limited efficacy of these agents and paucity of data comparing these various treatment options, participation in a clinical trial is encouraged whenever possible. Complete response rates in previously treated or relapsed MCL are generally low (<30%) and have limited response durations. Among patients who have disease progression after the receipt of Bruton’s kinase inhibitor (BTK) therapy, the reported objective response rate ranges from 25 to 42% and a median overall survival of 6 to 10 months with salvage therapies. Allogeneic stem-cell transplantation may be an option for selected patients. However, non-relapse-related mortality remains high at 10 to 24%.
While the clinical course of MCL is generally aggressive, a small proportion of patients with low stage and low-risk disease may have an indolent course, managed by observation, splenectomy, or treatment with alkylating agents analogous to the treatment of patients with small lymphocytic lymphoma or follicular lymphoma.

Summary of Evidence

Tisagenlecleucel (Kymriah™)

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, DBLCL 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 post-marketing 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 (Yescarta™)

For individuals who are adults with a histologically confirmed diagnosis of aggressive NHL (e.g., 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 an 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 post marketing 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.

Brexucabtagene Autoleucel (Tecartus™)

For individuals who are adults with relapsed or refractory mantle cell lymphoma, the evidence includes one phase II single-arm study. Relevant outcomes are overall survival, disease-specific survival, quality of life, treatment-related mortality and morbidity. ZUMA-2 study enrolled adult patients with relapsed refractory MCL who were heavily pre-treated. Of 74 patients enrolled, therapy was successfully manufactured for 71 (96%) and administered to 68 (92%). Results were reported for pre-specified 60 evaluable patients with a median follow-up (as of the July 24, 2019 data cutoff date) of 12.3 months (range, 7.0 to 32.3). The primary efficacy analysis demonstrated an objective response rate of 87% with a 62% rate of complete response. The median duration of response, progression-free survival and median overall survival (OS) were not reached. Fifty-seven percent of patients remained in remission at data cutoff, and the estimated 12-month PFS and OS rates were 61% and 83%, respectively. Among patients who have disease progression after Bruton’s kinase inhibitor therapy, the reported objective response rate ranges from 25 to 42% with a median overall survival of 6 to 10 months with salvage therapies. In the absence of randomized controlled trial, it is difficult to draw comparisons with currently available salvage treatment. No notable study limitations were identified. 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 ongoing and unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

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<th>NCT No.</th>
<th>Trial Name</th>
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<th>Completion Date</th>
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<td></td>
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<tr>
<td><strong>Tisagenlecleucel</strong></td>
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<tr>
<td>NCT02445248</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>NCT02445222</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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<td>NCT03876769</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>
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<td><strong>Axicabtagene ciloleucel</strong></td>
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<td>NCT02601313</td>
<td>A Phase 2 Multicenter Study Evaluating Subjects with Relapse/Refractory Mantle Cell Lymphoma (ZUMA-2)</td>
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<td>NCT02614066</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>NCT02625480</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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<td>NCT03105336</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>NCT02614066</td>
<td>A study evaluating brexucabtagene autoleucel in adult with r/r ALL</td>
<td>125</td>
<td>Aug 2020</td>
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### NCT No. | Trial Name | Planned Enrollment | Completion Date
---|---|---|---
NCT02625480* | Study evaluating brexucabtagene autoleucel in pediatric and adolescent participants with r/r ALL or r/r B-cell NHL | 116 | Aug 2023
NCT03624036* | Safety and Efficacy of brexucabtagene autoleucel in adults with r/r CLL | 108 | Mar 2021

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<td><strong>Tisagenlecleucel</strong></td>
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| NCT022828096* | 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 | 64 | May 2019

NCT: national clinical trial.

* Denotes industry-sponsored or cosponsored trial.

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**Practice Guidelines and Position Statements**

**National Comprehensive Cancer Network**

Current National Comprehensive Cancer Network (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.4.2020) 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.
Current NCCN guidelines for B-cell non-Hodgkin lymphoma (v.4.2020) recommend (category 2A) brexucabtagene autoleucel as a treatment option for adult patient with relapsed or refractory mantle cell lymphoma only after chemoimmunotherapy and BTK inhibitor.

**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.4.2020. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed September 2, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org.

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.

On July 24, 2020, brexucabtagene autoleucel (Tecartus™; Kite Pharma) was approved by the FDA for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).

**References**


### History

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<tr>
<td>07/01/20</td>
<td>New policy, approved June 9, 2020, created with literature review through July 2019. Add to Therapy section. FDA-approved tisagenlecleucel and axicabtagene ciloleucel therapies were moved from policy 8.01.01 Adoptive Immunotherapy to create this new standalone policy 8.01.63.</td>
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<tr>
<td>01/01/21</td>
<td>Coding update, Added HCPCS code C9073.</td>
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**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.
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  - 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

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  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 509F, HHH Building
  Washington, D.C. 20201, TTY 800-335-7585, Email OCRComplaints@HHS.gov

Getting Help in Other Languages

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