Introduction

The immune system is made up of a number of 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 treatment that draws on the immune system’s natural fighting ability is called chimeric antigen receptor (CAR) therapy. In this technique T-cells — a type of white blood cell — are withdrawn from the person to be treated. They’re re-engineered in a lab and given back to the patient. These treated cells are then able to better attack cancer cells. This policy describes when adoptive immunotherapy 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>Service</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kymriah™</td>
<td>Kymriah™ (tisagenlecleucel) intravenous infusion is considered</td>
</tr>
<tr>
<td>Service</td>
<td>Medical Necessity</td>
</tr>
<tr>
<td>---------</td>
<td>------------------</td>
</tr>
<tr>
<td>(tisagenlecleucel) intravenous infusion</td>
<td>medically necessary for relapsed(^a) or refractory(^b) B-cell acute lymphoblastic leukemia patients if they meet all of the following criteria:</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 25 years old or younger 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 not 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>o Burkitt lymphoma</td>
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<tr>
<td></td>
<td>o Active hepatitis B, C, or any uncontrolled infection</td>
</tr>
<tr>
<td></td>
<td>o Grade 2 to 4 graft-versus-host disease</td>
</tr>
<tr>
<td></td>
<td>o Concomitant genetic syndrome with the exception of Down syndrome</td>
</tr>
<tr>
<td></td>
<td>o Received allogeneic cellular therapy, such as donor lymphocyte infusion within 6 weeks prior to tisagenlecleucel infusion</td>
</tr>
<tr>
<td></td>
<td>o Active central nervous system disease</td>
</tr>
<tr>
<td></td>
<td>▪ Patients with central nervous system 2 disease (defined as having a WBC count of less than 5/mL and blasts on cytospin findings) are eligible.</td>
</tr>
</tbody>
</table>

\(^a\) 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).

Kymriah™ (tisagenlecleucel) intravenous infusion is considered medically necessary for adult patients with relapsed or refractory (r/r) large B-cell lymphoma including diffuse large...
<table>
<thead>
<tr>
<th>Service</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| **B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma if they meet all of the following criteria:**  
- Patient is ≥ 18 years of age  
- Patient has had two or more lines of systemic therapy including:  
  - rituximab and an anthracycline  
  **OR**  
  - has relapsed following autologous (not allogeneic) hematopoietic cell transplantation (HCT)  
- Patient does not have primary central nervous system lymphoma  
- ECOG performance status is 0 or 1  
- Creatinine clearance is ≥ 60 ml/min  
- Alanine aminotransferase (ALT) ≤ 5 times normal  
- Cardiac ejection fraction ≥ 45%  
- Absolute lymphocyte concentration ≥300/μL |

<table>
<thead>
<tr>
<th>Service</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| **Yescarta™ (axicabtagene ciloleucel)**  
  (axicabtagene ciloleucel) | **Yescarta™ (axicabtagene ciloleucel) may be medically necessary for adult patients with relapsed or refractory large B-cell lymphoma, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma if they meet all of the following criteria:**  
- Histologically confirmed diagnosis of one of the above  
- Have previously received two or more lines of systemic therapy  
- Are at least 18 years old  
- Do not have primary central nervous system lymphoma.  
- Refractory disease to the most recent therapy or relapse within 1 year after autologous hematopoietic stem cell transplantation (HSCT).  
- No prior allogeneic HSCT  
- ECOG performance status < 2 (see table below)  
- Absolute lymphocyte count ≥100/μL, |
<table>
<thead>
<tr>
<th>Service</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
|         | • Creatinine clearance ≥ 60 mL/min  
|         | • Hepatic transaminases ≤ 2.5 times upper limit of normal  
|         | • Ejection fraction ≥ 50%  
|         | • No active serious infection |

<table>
<thead>
<tr>
<th>Service</th>
<th>Investigational</th>
</tr>
</thead>
</table>
| CAR T-Cell therapies | Repeat treatment with a CAR T-Cell therapy is considered investigational.  
|         | All other uses of Kymriah, Yescarta or other chimeric antigen receptor T-cell therapies for conditions not outlined in this policy 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:  
- Office visit notes that contain the relevant history and physical and prior cancer treatment history.

**ECOG (Eastern Cooperative Oncology Group) Performance Scoring Criteria**

<table>
<thead>
<tr>
<th>ECOG</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Asymptomatic, no restrictions on activity</td>
</tr>
<tr>
<td>1</td>
<td>Symptomatic but completely ambulatory, able to do light or sedentary work</td>
</tr>
<tr>
<td>2</td>
<td>Symptomatic, &lt;50% in bed during the day, ambulatory and capable of all self-care but unable to carry out any work activities</td>
</tr>
<tr>
<td>3</td>
<td>Symptomatic, &gt;50% in bed, but not bedbound, only limited self-care, confined to bed or chair 50% or more of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Bedbound, completely disabled, unable to perform self-care</td>
</tr>
</tbody>
</table>

**Coding**
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J3590</td>
<td>Unclassified biologics</td>
</tr>
<tr>
<td>Q2040</td>
<td>Tisagenlecleucel (Kymriah™), up to 250 million car-positive viable T cells, including leukapheresis and dose preparation procedures, per infusion (new code effective 1/1/18)</td>
</tr>
<tr>
<td>Q2041</td>
<td>Axicabtagene ciloleucel (Yescarta™), up to 200 million autologous anti-CD19 CAR T Cells, including leukapheresis and dose preparation procedures, per infusion (new code effective 4/1/18)</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>
</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 Kymriah™ (tisagenlecleucel) for patients 50 kg or less is 0.2 to 5.0×10⁶ chimeric antigen receptor-positive viable T cells per kg body weight intravenously; for patients above 50 kg, dose is 0.1 to 2.5 x 10⁸ total chimeric antigen receptor-positive viable T cells (non-weight-based) 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)
Kymriah™ (tisagenlecleucel) and Yescarta™ (axicabtagene ciloleucel) have a black box warning because of the risk of cytokine release syndrome and neurologic toxicities that include fatal or life-threatening reactions. Neither of these should be administered to patients with active infection or inflammatory disorders. It is recommended that severe or life-threatening cytokine release syndrome should be treated with tocilizumab. Patients should be monitored for neurologic events after treatment.

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

- Health care facilities that dispense and administer tisagenlecleucel 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 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 are trained about the management of cytokine release syndrome and neurologic toxicities.

**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 immunologic therapies designed to stimulate a patient’s own immune system. Adoptive immunotherapy is a method of activating lymphocytes and/or other types of cells for the treatment of cancer and other diseases. Cells are removed from the patient, processed for some period of time, and then infused back into the patient.
Background

Adoptive Immunotherapy

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

T Lymphocytes and Killer Cells

Initially, this treatment was performed by harvesting peripheral lymphokine-activated killer cells and activating them in vitro 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 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. These factors limit the widespread applicability of TIL treatment. Recently, cytokine-induced killer cells have been recognized as a new type of anti-tumor effector cells, which can proliferate rapidly in vitro, with stronger anti-tumor activity and a broader spectrum of targeted tumors than other reported anti-tumor effector cells.¹

Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (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 3 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 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 a 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 2017 meta-analysis of 20 studies of 11,249 pediatric ALL, the hazard ratio for event-free survival in MRD-negative patients compared with MRD-positive patients was 0.23 (95% confidence interval, 0.18 to 0.28).³

Approximately 5000 cases of B-cell ALL are diagnosed every year in the United States,⁴ and approximately 620 pediatric and young adult patients with B-cell ALL will relapse each year in the United States.⁵ It 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.⁴ While it is treatable in 85% of cases, approximately 15% of children and young adults with ALL will relapse while 2% to 3% of ALL patients are primary refractory.⁶ Retreatment of refractory or relapsed ALL is generally unsuccessful and associated with a high mortality rate.⁷ The 2-year survival rate among patients with ALL who relapse after hematopoietic cell transplantation is 15%.⁸ The Food and Drug Administration 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 was 2.5 months and 6 months, and median overall survival durations were 3 months and 7.5 months, respectively.⁹,¹⁰ 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.

**Non-Hodgkin’s Lymphoma (NHL)**

A group of heterogeneous disorders involved in the proliferation of lymphoid cells. NHL is broadly categorized by cell-origin: B-cell lymphomas or NK/T-cell lymphomas. Additionally, NHLs can be characterized by aggressive (fast-growing) or indolent (slow-growing) subtypes. About 80-85% of NHL cases will arise from B-cells. Yescarta™ (axicabtagene ciloleucel) is approved by the FDA for three subtypes of NHL:
• **Diffuse large B-cell lymphoma (DLBCL)**
  This aggressive subtype of NHL often presents itself with enlarged lymph nodes that constitute a painless rapid swelling of the neck, abdomen, or groin area.

• **Primary Mediastinal B-cell lymphoma (PMBCL)**
  A rare form of DLBCL that arises exclusively from the thymus. PMBCL presents primarily as a mass in the mediastinum and is often associated with respiratory symptoms relating to its location that include SOB, pleural effusions, and superior vena cava syndrome.

• **Transformed Follicular lymphoma (TFL)**
  Follicular lymphoma (FL) is an indolent NHL subtype, but a number of patients will have their follicular lymphomas “transform” — in which they become aggressive forms of NHL. A classic example includes FL transforming into DLBCL.

Non-Hodgkin’s lymphoma accounts for about 4% of all cancers in the United States and is the most common cancer of the lymphatic system. In 2017, it is estimated that 72,240 people (40,080 males and 32,160 females) will have a diagnosis of NHL and 20,140 will die from the disease (11,450 males and 8,690 females). One of the most common subtypes of NHL include diffuse large B-cell lymphoma (DLBCL), which accounts for 1 out of every 3 lymphomas that are diagnosed in the United States. About 50-60% of patients with DLBCL will achieve CR after first-line therapy, 30-40% will relapse, and 10% will have refractory disease. The life expectancy of an individual who has r/r DLBCL is 3-4 months if left untreated. PMBCL occurs infrequently and accounts for 2% of all NHLs. Patients with PMBCL have cure rates of 80-85% with current therapies. The remaining 15-20% of patients will relapse (half cases are refractory) and follows within the first 6-12 months after post-treatment. Those with r/r PMBCL have poor prognosis rates. The disease also occurs more frequently in women in their 20s to 40s, with the median age being 35. About 1 of every 5 lymphomas in the United States will be diagnosed as FL. Histological transformation from FL to DLBCL occurs at an annual rate of ~ 3% for 15 years. After 15 years, the risk of transformation falls off, but the mechanism behind it is unclear. The five-year OS rate with limited transformation vs. advanced transformational disease was 66% and 9% respectively.

**DLBCL & PMBCL**

DLBCL patients can be subtyped through gene expression profiling (GEP). Germinal center B-cell (GCB) DLBCL has a profile that is representative of B-cells of the germinal center. Germinal centers (GCs) are structures in secondary lymphoid organs involved in the selection of B-cells that secrete high-affinity antibodies. The GC contains a dark zone that has a high density of
proliferating B-cells that undergo immunoglobulin somatic hypermutation (SHM). The light zone is the selection of B-cells in the presence of follicular dendritic cells (FDC), T-cells, and macrophages. Activated B-cell (ABC) DLBCL is believed to be derived from B-cells that are differentiating from GCBs to plasma cells. Primary mediastinal large B-cell lymphoma (PMBCL) ascends from thymic B-cells. Patients with T cell/histiocyte-rich large B-cell lymphomas (T/HRLBL) have a T-cell rich background that contain scattered large B-cells and histiocytes. This lymphoma likely arises from a progenitor cell of the germinal cell origin. Further discussion of T/HRLBL is out of the scope of this monograph, but relays the complexity of the NHLs and their subtypes. NCCN guidelines however do not recommend GEP for routine clinical, since the treatment algorithms are the same for patients who have GCB or non-GCB DLBCL subtypes. There is current controversy on what is optimal first-line treatment for PMBCL due to the limited data available.

**TFL**

FL is a lymphoma that is derived from follicle center B-cells. The pathophysiology in which FL turns into TFL is largely unknown. It is challenging to predict the timing of possible transformation during onset of FL, and there are no known risk factors that may be associated with increased transformation such as age group or gender.

**Kymriah™ (tisagenlecleucel)**

Kymriah™ (tisagenlecleucel) is an adoptive immunotherapy in which T cells of a patient are modified by genetic engineering using 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 targets and binds 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.
**Genetically Engineered T Cells**

**Peripheral T Lymphocytes**

For individuals with cancers who receive autologous peripheral T lymphocytes containing tumor antigen-specific T-cell receptors, the evidence includes multiple small observational studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Multiple observational studies have examined autologous peripheral T lymphocytes containing tumor antigen-specific T-cell receptors in melanoma, Hodgkin and non-Hodgkin lymphoma, prostate tumors, and neuroblastoma. Because of the noncomparative nature of the available evidence with a small sample size, it is difficult to draw any meaningful conclusion. To establish efficacy, the following is needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Summary of Evidence**

**Kymriah™ (tisagenlecleucel)**

For individuals who are 3 to 25 years of age with relapsed or refractory B-cell acute lymphoblastic leukemia who receive Kymriah™ (tisagenlecleucel), the evidence includes multiple single-arm prospective trials. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The pivotal single-arm trials reported an 83% response rate (measured by complete response or complete remission with incomplete blood count) in heavily pretreated patients. All patients who achieved a complete remission or complete remission with incomplete blood count were also minimal residual disease-negative, which is predictive of survival in acute lymphoblastic leukemia patients. After a median follow-up of 4.8 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 reactions. Cytokine release syndrome was observed in more than half (63%) of the patients, and approximately 40% had an adverse event at grade 4 or higher. Long-term follow-up and real-world evidence is required to assess the generalizability of tisagenlecleucel efficacy and safety outside of a clinical trial setting. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.
For adults with ge with relapsed or refractory DLBCL, evidence includes an open label multicenter single arm trial of 160 patients. Subject had received ≥ 2 lines of chemotherapy, including rituximab and anthracycline, or relapsed following autologous hematopoietic stem cell transplantation (HSCT). The study excluded patients with active central nervous system malignancy, prior allogenic HSCT, an ECOG performance status ≥ 2, a creatinine clearance < 60, alanine aminotransferase > 5 times normal, cardiac ejection fraction < 45%, or absolute lymphocyte concentration less than 300/μL.

Kymriah was infused following lymphodepleting (LD) chemotherapy with either fludarabine /cyclophosphamide or bendamustine. The efficacy outcomes were objective response, as assessed by an independent review committee, and duration of response.

Of the 160 patients, 106 received tisagenlecleucel, 11 did not due to manufacturing failure. Thirty-eight others did not receive tisagenlecleucel, due to death (n = 16), physician decision (n = 16), or adverse events (n = 3).

Of the 92 patients receiving KYMRIAH manufactured in the US, 90% received physician’s choice of bridging chemotherapy in the interval between start of screening and KYMRIAH infusion. A retrospectively identified sub-group of 68 was evaluable. Among the efficacy evaluable population of 68 patients, median time to first response (CR or PR) was 0.9 months (0.7 to 3.3). median duration of response was not reached. Response was longer in patients who achieved CR. Of the 22 patients who experienced a CR, 9 achieved this status by 1 month, 12 more by month 3, and the last by month 6 after KYMRIAH infusion. ORR response was 34 (50%). CR 22 (32%),

**Yescarta™ (axicabtagene ciloleucel)**

Yescarta™ (axicabtagene ciloleucel) is the 2nd FDA approved CAR T-cell therapy approved, following Novartis’ Kymriah™ (tisagenlecleucel). Axicabtagene ciloleucel is a CD19-directed immunotherapy that utilizes the patient’s own T-cells to target CD19 expressing cancer and normal B cells. Adult patients who have r/r DLBCL, PMBCL, or TFL have poor outcomes. The ZUMA-1 trial showed ORR of 72%, with patients achieving CR at 51%. Many of these patients have gone through a median number of 3 prior therapies before axi-cel administration. Through the ZUMA-1 trial, 94% of patients observed had CRS, with 13% being a Grade 3 or higher. There were 31% of patients who experienced neurological toxicities that were a Grade 3 or above. Due to these toxicities, axicabtagene ciloleucel is only available through YESCARTA REMS. There is a need for long-term studies of efficacy and safety in order to establish where this product will fit in the treatment algorithm.
Ongoing and Unpublished Clinical Trials

Some 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>Cytotoxic T lymphocytes</strong></td>
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</tr>
<tr>
<td>NCT02227641</td>
<td>Preventative/Preemptive Adoptive Transfer of Peptide Stimulated CMV/EBV Specific T-cells in Patients After Allogeneic Stem Cell Transplantation</td>
<td>50</td>
<td>Mar 2017 (ongoing)</td>
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<tr>
<td><strong>Lymphokine-activated killer cells</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02118415</td>
<td>Targeted Natural Killer (NK) Cell Based Adoptive Immunotherapy for the Treatment of Patients With Non-Small Cell Lung Cancer (NSCLC) After Radiochemotherapy (RCT)</td>
<td>90</td>
<td>Feb 2018</td>
</tr>
<tr>
<td>NCT02229266</td>
<td>Randomised Controlled Phase-2 Trial to Determine the Efficacy of Adoptive Immunotherapy With NK Cells in High-risk AML (HINKL)</td>
<td>56</td>
<td>Sep 2019</td>
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<tr>
<td><strong>Tumor-infiltrating lymphocytes</strong></td>
<td></td>
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<td></td>
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<tr>
<td>NCT01319565</td>
<td>Prospective Randomized Study of Cell Therapy for Metastatic Melanoma Using Short-Term Cultured Tumor Infiltrating Lymphocytes Plus IL-2 Following Either a Non-Myeloablative Lymphocyte Depleting Chemotherapy Regimen Alone or in Conjunction w/1200 TBI</td>
<td>102</td>
<td>Jun 2020</td>
</tr>
<tr>
<td>NCT01966289</td>
<td>SGI-110 in Combination With an Allogeneic Colon Cancer Cell Vaccine (GVAX) and Cyclophosphamide (CY) in Metastatic Colorectal Cancer (mCRC)</td>
<td>32</td>
<td>Dec 2019</td>
</tr>
<tr>
<td>NCT01993719</td>
<td>A Phase II Prospective Randomized Study of Cell Transfer Therapy for Metastatic Melanoma Using Tumor Infiltrating Lymphocytes Plus IL-2 Comparing Two Different Chemotherapy Preparative Regimens</td>
<td>120</td>
<td>Sep 2019</td>
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<tr>
<td>NCT01995344</td>
<td>TIL Therapy in Metastatic Melanoma and IL2 Dose Assessment (METILDA)</td>
<td>90</td>
<td>Dec 2018</td>
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<tr>
<td>NCT No.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
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<tr>
<td>NCT02278887</td>
<td>Study Comparing TIL to Standard Ipilimumab in Patients With Metastatic Melanoma (TIL)</td>
<td>162</td>
<td>Sep 2020</td>
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</tbody>
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**Autologous dendritic cells**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00045968&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Study of a Drug [DCVax®-L] to Treat Newly Diagnosed GBM Brain Cancer</td>
<td>348</td>
<td>Nov 2016 (ongoing)</td>
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<tr>
<td>NCT00338377&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Lymphodepletion Plus Adoptive Cell Transfer With or Without Dendritic Cell Immunization</td>
<td>189</td>
<td>Feb 2019</td>
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<tr>
<td>NCT01204684</td>
<td>Dendritic Cell Vaccine for Patients With Brain Tumors</td>
<td>60</td>
<td>Sep 2017</td>
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**Dendritic cells/cytokine-induced killer cells**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tbody>
<tr>
<td>NCT01691625&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Concurrent Chemoradiation With or Without DC-CIK Immunotherapy in Treating Locally Advanced Esophageal Cancer</td>
<td>50</td>
<td>Sep 2019</td>
</tr>
<tr>
<td>NCT02202928</td>
<td>Adoptive Cell Therapy Plus Chemotherapy and Radiation After Surgery in Treating Patients With Colorectal Cancer</td>
<td>60</td>
<td>Dec 2017</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

**Practice Guidelines and Position Statements**

Current NCCN guidelines<sup>70</sup> for acute lymphoblastic leukemia recommend (category 2A) Kymriah™ (tisagenlecleucel) as a treatment option for:

- Ph-positive patients 25 years or less in age with refractory disease or 2 or greater relapses and failure of 2 tyrosine kinase inhibitors.
- Ph-negative patients 25 years or less in age with refractory disease or 2 or greater relapses.

**Medicare National Coverage**

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.
Regulatory Status

On August 30, 2017, tisagenlecleucel (Kymriah™; Novartis) was approved by the Food and Drug Administration 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 October 18, 2017, axicabtagene ciloleucel (Yescarta™; Kite/Gilead) was approved by the Food and Drug Administration for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

References


### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/01/18</td>
<td>New policy, approved December 12, 2017. Add to Prescription Drug section. Kymriah™ (tisagenlecleucel) and Yescarta™ (axicabtagene ciloleucel) are considered medically necessary when criteria are met. All other uses of Kymriah, Yescarta or other chimeric antigen receptor T-cell therapies for conditions not outlined in this policy are considered investigational.</td>
</tr>
<tr>
<td>03/01/18</td>
<td>Annual Review, approved February 6, 2018. No changes made to the policy statements.</td>
</tr>
<tr>
<td>04/01/18</td>
<td>Coding update, added HCPCS code Q2041 (new code effective 4/1/18).</td>
</tr>
<tr>
<td>05/21/18</td>
<td>Interim Review, approved May 18, 2018. Kymriah indications expanded to include treatment of relapsed/refractory large B-cell lymphoma (DLBCL) in adults per FDA approval 5/1/18.</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). ©2018 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 (TTY)
Email AppealsDepartmentInquiries@Premera.com

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).

Arabic (Arabic):

بيحوي هذا الإشعار معلومات هامة. قد يحتوي هذا الإشعار معلومات متعلقة بصحة ضيف طبي أو معلومات عن خطط Premera Blue Cross. إن تكون هناك إرشادات متعلقة بـ Premera Blue Cross في هذا الإشعار. سيتم إنشاء استمارة للإبلاغ عن إشادة المطلوبة. يكون كلو الحصص على هذه المعلومات والمساعدتان بخطوات تدور فيها الإرشادات. إذا استمارة الاستمارة

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

中文 (Chinese):

本通知有重要之訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險之重要訊息。本通知可能有重要日期。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).

Oromoo (Cushite):


Français (French):


Kreyòl ayisyen (Creole):


Deutsche (German):


Hmoob (Hmong):

Tsaab ntawv tsjaj xo no muaj cov ntsiab lus tseem ceeb. Tej zaum tsab ntawv tsjaj xo no muaj cov ntsiab lus tseem ceeb xog koi daim ntawv thov kev pab los yoj kog chov kev pab cuam los ntawm Premera Blue Cross. Tej zaum muaj cov hnuv tseem ceeb usas rau hauv daim ntawm no. Tej zaum koi juj yuav tau ua qee yam us peb koi us tis puub hauv cov cajj yuuy xog tseeg rau hauv daim ntawv no mas koi juj yuav tau baas kev pab cuam kho hauv yoj kev pab them tej nqi kho mib ntawv. Koi muaj cai kom lawv muab cov ntsiab lus no us taw muab sau uu koi hom lus pub daww rau koi. Hu rau 800-722-1471 (TTY: 800-842-5357).

Iloko (Ilocano):

Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaar mabalin nga adda ket naglaon iti napateg nga impormasion maianggep iti aplikasyon yowo coverage babaen iti Premera Blue Cross. Daytoy ket mabalin dagiti importante a pelta iti daytoy a pakdaar. Mabalin nga adda rumeng nga aramideng nga addang sakbay dagiti partikular a naatidung nga adda aldaw tapno manapatgalaidneyo ti coverage ti salun-ayno yowo tunglog kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tunglog iti bukodo a pagasasao nga awan ti bayadapti. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):

한국어 (Korean):
본 통지서에는 중요한 정보가 들어 있습니다. 즉 이 통지서는 귀하와 Premera Blue Cross를 통해 커버리지에 관한 정보를 포함하고 있습니다. 본 통지서에는 필요성이 되는 날짜들에 있을 수 있습니다. 귀하는 귀하의 건강 커버리지를 제공하는 기관이나 보험사를 찾아보고자 할 경우에만 접근할 수 있습니다. 귀하의 이러한 정보는 귀하의 만족도와 비용 부담이 없을 수 있는 권리가 있습니다. 800-722-1471 (TTY: 800-842-5357)로 전화하시오.

Polski (Polish):

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 e ajuda de custos. Vocês têm o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

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 claras 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):

ไทย (Thai):
ประกาศนี้มีข้อมูลสำคัญ ประกาศนี้มีข้อมูลสำคัญเกี่ยวกับการขอรับการส่งเสริมสุขภาพของคุณ Premera Blue Cross และการมีส่วนร่วมในการดูแลสุขภาพของคุณ คุณควรตรวจสอบข้อมูลนี้ในจากข้อมูลนี้เพื่อใช้งาน โดยติดต่อ Premera Blue Cross.

Український (Ukrainian):
Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страхувального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує можливість того, що Вам треба буде здійснити певні кроки у конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дзвоніть за номером телефону 800-722-1471 (TTY: 800-842-5357).

Tiếng Việt (Vietnamese):

日本語 (Japanese):
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