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 In this technique, certain types of immune system cells are withdrawn from the person to be treated.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>Kymriah™ (tisagenlecleucel)</td>
<td>Kymriah™ (tisagenlecleucel) intravenous infusion is considered medically necessary for relapsed(^a) or refractory(^b) patients if they meet all of the following criteria:</td>
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<tr>
<td></td>
<td>• Confirmed diagnosis of CD19-positive B-cell acute lymphoblastic leukemia with morphologic bone marrow tumor involvement (≥5% lymphoblasts)</td>
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<td></td>
<td>• Are up to 25 years old at the time of infusion</td>
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<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>
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<tr>
<td></td>
<td>• Have adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis</td>
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<td>• Do not have any of the following:</td>
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<tr>
<td></td>
<td>o Burkitt lymphoma</td>
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<td></td>
<td>o Active hepatitis B, C, or any uncontrolled infection</td>
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<td></td>
<td>o Grade 2 to 4 graft-versus-host disease</td>
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<td>o Concomitant genetic syndrome with the exception of Down syndrome</td>
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<td></td>
<td>o Received allogeneic cellular therapy, such as donor lymphocyte infusion, within 6 weeks prior to tisagenlecleucel infusion</td>
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<tr>
<td></td>
<td>o Patient has 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).</td>
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</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>
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<tbody>
<tr>
<td><strong>Yescarta™ (axicabtagene ciloleucel)</strong></td>
<td><strong>Yescarta™ (axicabtagene ciloleucel) or Kymriah™ (tisagenlecleucel) intravenous infusion (except as indicated⁵) is considered medically necessary for relapsed or refractory⁶ patients if they meet all of the following criteria:</strong></td>
</tr>
<tr>
<td><strong>Kymriah™ (tisagenlecleucel)</strong></td>
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<tr>
<td></td>
<td>• Are adults (age ≥18) at the time of infusion</td>
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<tr>
<td></td>
<td>• Histologically confirmed diagnosis of diffuse large B-cell lymphoma, not otherwise specified; or primary mediastinal large B-cell lymphoma⁴ or high-grade B-cell lymphoma or diffuse large B-cell lymphoma arising from follicular lymphoma</td>
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<tr>
<td></td>
<td>• Received adequate prior therapy including all of the following:</td>
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<tr>
<td></td>
<td>o Anti-CD20 monoclonal antibody for CD20-positive tumor</td>
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<tr>
<td></td>
<td>o Anthracycline-containing chemotherapy regimen</td>
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<tr>
<td></td>
<td>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</td>
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<td>• Have adequate organ and bone marrow function as determined by the treating oncologist/hematologist</td>
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<td></td>
<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>
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<td></td>
<td><strong>AND</strong></td>
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<td></td>
<td>• Do not have primary central nervous system lymphoma</td>
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<tr>
<td></td>
<td><strong>Note:</strong> ⁴ Tisagenlecleucel intravenous infusion is considered investigational for the treatment of relapsed or refractory primary mediastinal large B-cell lymphoma.</td>
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<tr>
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<td>⁶ 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).</td>
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</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Investigational</th>
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<tbody>
<tr>
<td><strong>Other applications</strong></td>
<td><strong>Other applications of adoptive immunotherapy are considered investigational.</strong></td>
</tr>
</tbody>
</table>
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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<tbody>
<tr>
<td></td>
<td><strong>CPT</strong></td>
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<tr>
<td>36511</td>
<td>Therapeutic apheresis; for white blood cells</td>
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<tr>
<td></td>
<td><strong>HCPCS</strong></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 (code terminated 1/1/19)</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 (new code effective 1/1/19)</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></td>
<td><strong>Non-Covered</strong></td>
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<tr>
<td></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 (new code effective 1/1/19)</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) (new code effective 1/1/19)</td>
</tr>
<tr>
<td>0539T</td>
<td>Chimeric antigen receptor T-cell (CAR-T) therapy; receipt and preparation of CAR-T cells for administration (new code effective 1/1/19)</td>
</tr>
<tr>
<td>0540T</td>
<td>Chimeric antigen receptor T-cell (CAR-T) therapy; CAR-T cell administration, autologous (new code effective 1/1/19)</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 a pheresis 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 5.0×10^6 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 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

**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 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 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 meta-analysis of 20 studies of 11,249 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). 

Approximately 5000 cases of B-cell ALL are diagnosed every year in the United States, and approximately 620 pediatric and young adult patients with B-cell ALL will relapse each year in the United States. 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.

**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. Retreatment of refractory or relapsed ALL is generally unsuccessful and associated with a high mortality rate. The 2-year survival rate among patients with ALL who relapse after hematopoietic cell transplantation is 15%. 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. 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**

Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin lymphoma and accounts for approximately 25% of non-Hodgkin lymphoma cases. 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 27,650 new cases of DLBCL were diagnosed in the United States in 2016.\textsuperscript{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%.\textsuperscript{11} However, based on a number of prognostic factors, 20% to 50% of DLBCL cases are refractory or relapse after first-line chemotherapy.\textsuperscript{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.\textsuperscript{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.

**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 (DC) that have been pulsed with tumor antigens. Alternatively, innate tumor-infiltrating lymphocytes (TIL) from the tumor biopsy are propagated in vitro with interleukin-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.\textsuperscript{15}

**Cellular Therapy and Dendritic Cell Infusions**

The major research challenge in adoptive immunotherapy is to develop immune cells with anti-tumor reactivity in quantities sufficient for transfer to tumor-bearing patients. In current trials, two methods are studied: adoptive cellular therapy and antigen-loaded dendritic cell infusions.

Adoptive cellular therapy is "the administration of a patient’s own (autologous) or donor (allogeneic) anti-tumor lymphocytes following a lymphodepleting preparative regimen."\textsuperscript{16} Protocols vary, but include these common steps:

1. Lymphocyte harvesting (either from peripheral blood or from tumor biopsy)
2. Propagation of tumor-specific lymphocytes in vitro using various immune modulators
3. Selection of lymphocytes with reactivity to tumor antigens with enzyme-linked immunosorbent assay
4. Lymphodepletion of the host with immunosuppressive agents
5. Adoptive transfer (ie, transfusion) of lymphocytes back into the tumor-bearing host

DC-based immunotherapy uses autologous DC (ADC) to activate a lymphocyte-mediated cytotoxic response against specific antigens in vivo. ADCs harvested from the patient are either pulsed with antigen or transfected with a viral vector bearing a common cancer antigen. The activated ADCs are then retransfused back into the patient, where they present antigen to effector lymphocytes (CD4-positive T cells, CD8-positive T cells, and in some cases, B cells). This initiates a cytotoxic response against the antigen and against any cell expressing the antigen. In cancer immunotherapy, ADCs are pulsed with tumor antigens; effector lymphocytes then mount a cytotoxic response against tumor cells expressing these antigens (see Related Policies for dendritic cell-based immunotherapy for prostate cancer).

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

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

**Tisagenlecleucel**

Tisagenlecleucel is an 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.\(^{17}\)

**Axicabtagene Ciloleucel**

Similar to tisagenlecleucel, axicabtagene ciloleucel is an 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.\(^{18}\)
Summary of Evidence

Cytotoxic T Lymphocytes

For individuals with Epstein-Barr virus (EBV)-associated cancers who receive cytotoxic T lymphocytes (CTL), the evidence includes two small, prospective noncomparative cohort studies. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The cohort studies have shown a treatment response to infused cytotoxic T lymphocytes directed against cancer-associated viral antigens. To establish efficacy, the following are needed: large, 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.

For individuals with Cytomegalovirus-associated cancers who receive CTL, the evidence includes a single case series. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. In the absence of an RCT comparing CTL with the standard of care, no conclusions can be made. To establish efficacy, the following are 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.

Cytotoxic-Induced Killer Cells

For individuals with nasopharyngeal carcinoma who receive CIK cells, the evidence includes a single RCT. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The RCT reported a numerically favorable but statistically insignificant effect on progression-free survival and overall survival. To establish efficacy, the following are 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.

For individuals with renal cell carcinoma (RCC) who receive CIK cells, the evidence includes multiple RCTs. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The largest of the RCTs reported statistically significant gains in progression-free survival and overall survival with CIK cell-based
immunotherapy compared with interleukin-2 plus interferon-α-2. This body of evidence is limited by the context of the studies (non-U.S.) and choice of a nonstandard comparator. The other two RCTs have also reported response rates in favor of CIK therapy with inconsistent effect on survival. To establish efficacy, the following are 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.

For individuals with gastric cancer who receive CIK cells, the evidence includes a single nonrandomized prospective study. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The prospective cohort study reported statistically significant effects on disease-free survival and overall survival in favor of immunotherapy vs no immunotherapy. To establish efficacy, the following are 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.

For individuals with colorectal cancer who receive CIK cells, the evidence includes a single RCT and one cohort study. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Results of the RCT showed a statistically significant effect on overall survival in favor of immunotherapy vs chemotherapy alone. To establish efficacy, the following are 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.

For individuals with hepatocellular carcinoma who receive CIK cells, the evidence includes several RCTs. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Several RCTs from Asia have generally reported some benefits in response rates and/or survival. The results of a meta-analysis of these trials have also shown a statistically significant 41% reduction in the hazard of death, but there was considerable heterogeneity across the included studies. This body of evidence is limited by the context of the studies (non-U.S.), small sample sizes, heterogeneous treatment groups, and other methodologic weaknesses. To establish efficacy, the following are 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.
For individuals with non-small-cell lung cancer (NSCLC) who receive CIK cells, the evidence includes multiple RCTs and a systematic review. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. A single systematic review of RCTs reported some benefits in median time to progression and median survival time. The trials assessed in the systematic review were limited by the context of the studies (non-U.S.), small sample sizes, heterogeneous treatment groups, and other methodologic weaknesses. To establish efficacy, the following are 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.

**Tumor-Infiltrating Lymphocytes**

For individuals with melanoma who receive tumor-infiltrating lymphocytes (TIL), the evidence includes a single RCT. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Results of a small RCT have reported no difference in relapse or survival outcomes. Cohort studies in patients with refractory metastatic melanoma have demonstrated response rates of 49% with immunotherapy and 52% to 72% with no immunotherapy. To establish efficacy, the following are 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.

**Dendritic Cells**

For individuals with glioblastoma multiforme who receive dendritic cells (DC), the evidence includes a systematic review of observational studies. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Because of the observational and noncomparative nature of the available evidence, it is difficult to draw any meaningful conclusions. To establish efficacy, the following are 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. Interim results from one such RCT have been published but are not informative because the patients were unblinded and results combined for the treatment and
placebo arms. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with non-small-cell lung cancer who receive dendritic cells, the evidence includes two RCTs and a meta-analysis. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The RCTs have generally reported some benefits in response rates and/or survival. The meta-analysis of these trials also reported a statistically significant reduction in the hazard of death. Most trials were from Asia and did not use standard of care as the control arm. This body of evidence is limited by the context of the studies (non-U.S.), small sample sizes, heterogeneous treatment groups, and other methodologic weaknesses. To establish efficacy, the following are 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.

For individuals with medullary thyroid cancer who receive dendritic cells, the evidence includes one prospective noncomparative study. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. A small prospective noncomparative study in ten medullary thyroid cancer patients treated with autologous dendritic cells has been published. There are no RCTs comparing dendritic cell-based adoptive immunotherapy with standard of care and, therefore, no conclusions can be made. To establish efficacy, the following are 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.

For individuals with pancreatic cancer who receive dendritic cells, the evidence includes a small prospective noncomparative study. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The study reported on treatment outcomes for five patients with pancreatic cancer. Because of the noncomparative nature of the available evidence and small sample base, it is difficult to draw any meaningful conclusions. To establish efficacy, the following are 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.
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. The 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 and a small sample size, it is difficult to draw any meaningful conclusion. To establish efficacy, the following are 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.

Tisagenlecleucel

For individuals who are up to 25 years of age with relapsed or refractory B-cell acute lymphoblastic leukemia who receive tisagenlecleucel, the evidence includes multiple single-arm prospective trials. The 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 events. 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 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 non-Hodgkin lymphoma (eg, diffuse large B-cell lymphoma 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 overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The pivotal single-arm trial reported a 50% overall response rate (measured by complete or partial remission) in heavily pretreated patients. After a median follow-up of 9.4 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 cytokine release syndrome was observed in 74% of the patients, and 23% had grade 3 or higher cytokine release syndrome. 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 non-Hodgkin lymphoma (eg, diffuse large B-cell lymphoma 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 overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The pivotal single-arm trial reported a 72% overall response rate (measured by complete or partial remission) in heavily pretreated patients. After a median follow-up of 7.9 months, the median duration of response was 9.2 months. The observed benefits were offset by a high frequency and severity of adverse events. Cytokine release syndrome was observed in more than half (63%) of the patients, and 44% 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 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>Cytotoxic induced killer cells</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 (ongoing)</td>
</tr>
<tr>
<td>NCT02118415</td>
<td>Randomized 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 2020</td>
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</tbody>
</table>

**Tumor-infiltrating lymphocytes**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<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>64</td>
<td>Sep 2029</td>
</tr>
<tr>
<td>NCT01966289</td>
<td>A Pilot Study of SGI-110 in Combination With an Allogeneic Colon Cancer Cell Vaccine (GVAX) and Cyclophosphamide (CY) in Metastatic Colorectal Cancer (mCRC) as Maintenance Therapy</td>
<td>18</td>
<td>Dec 2019</td>
</tr>
<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>NCT02278887</td>
<td>Randomized Phase III Study Comparing a Non-myeloablative Lymphocyte Depleting Regimen of Chemotherapy Followed by Infusion of Tumor Infiltrating Lymphocytes and Interleukin-2 to Standard Ipilimumab Treatment in Metastatic Melanoma</td>
<td>168</td>
<td>Sep 2020</td>
</tr>
</tbody>
</table>

**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>NCT00338377a</td>
<td>Lymphodepletion Plus Adoptive Cell Transfer With or Without Dendritic Cell Immunization</td>
<td>189</td>
<td>Feb 2019</td>
</tr>
<tr>
<td>NCT01204684</td>
<td>A Phase II Clinical Trial Evaluating Autologous Dendritic Cells Pulsed With Tumor Lysate Antigen +/- Toll-like Receptor Agonists for the Treatment of Malignant Glioma</td>
<td>60</td>
<td>Oct 2019</td>
</tr>
</tbody>
</table>

**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>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01691625a</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>NCT No.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
</tr>
<tr>
<td>-----------</td>
<td>-------------------------------------------------------------------------------------------------------</td>
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<td>------------------</td>
</tr>
<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 (DLBCL)</td>
<td>116</td>
<td>Feb 2023</td>
</tr>
<tr>
<td>NCT02228096</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 (DLBCL)</td>
<td>64</td>
<td>Dec 2022</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>
</tr>
</tbody>
</table>

### Practice Guidelines and Position Statements

Current guidelines from the National Comprehensive Cancer Network do not include recommendations for adoptive immunotherapy to treat cancers of the bladder, head and neck, hepatobiliary system, kidney, pancreatic, stomach, thyroid, melanoma, Hodgkin lymphoma, or non-small-cell lung cancer.

Current National Comprehensive Cancer Network guidelines for acute lymphoblastic leukemia 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 lymphomas recommend (category 2A) axicabtagene ciloleucel or tisagenlecleucel as a treatment option.

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

Medicare National Coverage

There is no national coverage determination.

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 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 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.

References


71. AMCP Formulary Dossier Version 4: Kymriah (Tisagenlecleucel[CTL019]): Version Date: May 2018.


**History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>01/97</td>
<td>Add to Therapy Section - New Policy</td>
</tr>
<tr>
<td>05/19/98</td>
<td>Replace policy. Policy updated; new indications</td>
</tr>
<tr>
<td>12/10/02</td>
<td>Replace policy. Policy updated; new references added. No change in policy statement.</td>
</tr>
<tr>
<td>04/15/03</td>
<td>Replace policy. Policy reviewed with CPT codes added. No change in policy statement.</td>
</tr>
<tr>
<td>01/01/04</td>
<td>Replace policy. CPT code updates only.</td>
</tr>
<tr>
<td>05/11/04</td>
<td>Replace policy. Policy updated; no change in policy statement. Additional discussion of dendritic cell therapy.</td>
</tr>
<tr>
<td>06/14/05</td>
<td>Replace policy. Policy updated with literature search; no change in policy statement.</td>
</tr>
<tr>
<td>02/06/06</td>
<td>Codes Updated. No other changes.</td>
</tr>
<tr>
<td>06/16/06</td>
<td>Replace policy. Policy updated with literature search; no change in policy statement;</td>
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<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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<tr>
<td>06/12/07</td>
<td>Replace policy. Policy updated; no change in policy statement. Reviewed and recommended by OAP on May 24, 2007.</td>
</tr>
<tr>
<td>01/13/09</td>
<td>Replace policy. Policy updated with literature search. Policy statement updated to include “adoptive cellular therapy (ACT) for the administration of lymphokine-activated killer cells (LAK) tumor-infiltrating lymphocytes (TIL), or antigen-loaded dendritic cells (ADCs)” as an investigational indication. Investigational statement deleted. References added. Reviewed and recommended by OAP on August 21, 2008.</td>
</tr>
<tr>
<td>12/08/09</td>
<td>Cross Reference Update - No other changes.</td>
</tr>
<tr>
<td>05/11/10</td>
<td>Cross Reference Update - No other changes.</td>
</tr>
<tr>
<td>06/13/11</td>
<td>Replace policy. Policy updated with literature search; reference numbers 33–48 added; no change in policy statements. ICD-10 codes added to policy.</td>
</tr>
<tr>
<td>02/14/12</td>
<td>Replace policy. Policy updated with literature search; references 23 and 24 added and other references renumbered or removed. No change in policy statements.</td>
</tr>
<tr>
<td>08/15/12</td>
<td>Update Related Policies: remove 2.03.04, as it was archived.</td>
</tr>
<tr>
<td>09/28/12</td>
<td>Update Coding Section – ICD-10 codes are now effective 10/01/2014.</td>
</tr>
<tr>
<td>02/13/13</td>
<td>Replace policy. Policy updated with literature search; Two systematic reviews added; Primary studies added on cytokine-induced killer (CIK) cells; references 1, 3–6, 24, and 27 added and other references renumbered. The wording of the policy statement under adoptive cellular therapy was changed to include cytokine-induced killer (CIK) cells; however, the intent of both policy statements (i.e., investigational) is unchanged. Remove Related Policy 2.03.500 as it was archived.</td>
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<tr>
<td>07/25/13</td>
<td>Update Related Policies. Add 8.01.520.</td>
</tr>
<tr>
<td>02/24/14</td>
<td>Replace policy. Policy updated with literature search through November 8, 2013; references 3, 8, 27, and 31 added. No change in policy statements.</td>
</tr>
<tr>
<td>02/25/15</td>
<td>Annual Review. Policy updated with literature review through November 2, 2014; references 6–9, 12, 14–17, 41, 46, 52–53, and 56–65 added; reference 55 updated. Rationale reorganized and references renumbered. Cytotoxic T-lymphocytes and genetically engineered T cells added to investigational policy statements; “autologous” added to clarify antigen-loaded dendritic cells. ICD-9 and ICD-10 codes removed; these are not utilized in policy adjudication.</td>
</tr>
<tr>
<td>02/09/16</td>
<td>Annual Review. Policy updated with literature review through November 10, 2015; references 13 and 17–18 added. Section on lymphokine-activated killer cell deleted as this is an obsolete intervention. Policy statements unchanged.</td>
</tr>
<tr>
<td>01/01/18</td>
<td>Annual Review, approved December 12, 2017. Policy updated with literature review through April 2017. Policy statement changed for clarity as Kymriah™ (tisagenlecleucel) and Yescarta™ (axicabtagene ciloleucel) are addressed in policy 5.01.580. Removed codes 96365, 96367, 96368, and S2107.</td>
</tr>
</tbody>
</table>
### Date | Comments
--- | ---
11/01/18 | Annual Review, approved October 19, 2018. Policy criteria for Chimeric Antigen Receptor (CAR) T Cell Therapies is now addressed in this policy; added codes J3590, Q2040, Q2041, S2107. Removed CPT code 37799. Policy 5.01.580 is now deleted. Policy updated with literature review through June 2018; several references added.
11/17/18 | Minor update, added Documentation Requirements section.
01/01/19 | Coding update, added 0537T, 0538T, 0539T, 0540T, and Q2042 (new codes effective 1/1/19).
04/01/19 | Annual Review, approved March 19, 2019. Policy updated with literature review through October 2018; reference 31 added. Policy statements unchanged.

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  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
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  - Qualified interpreters
  - Information written in other languages

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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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