**Chimeric Antigen Receptor Therapy for Hematologic Malignancies**

**Policy Number:** 8.01.63  
**Last Review:** 12/2019  
**Origination:** 12/2019  
**Next Review:** 12/2020

**Policy**
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Chimeric Antigen Receptor Therapy for Hematologic Malignancies when it is determined to be medically necessary because the criteria shown below are met.

**When Policy Topic is covered or not covered**
Chimeric antigen receptor T-cell (CAR-T) therapy with tisagenlecleucel intravenous infusion is considered **medically necessary** for relapsed\(^a\) or refractory\(^b\) patients with B-cell acute lymphoblastic leukemia if they meet all of the following criteria:

- Confirmed diagnosis of CD19-positive B-cell acute lymphoblastic leukemia with morphologic bone marrow tumor involvement (≥5% lymphoblasts)
- Are up to 25 years old at the time of infusion
- Have not received prior treatment with tisagenlecleucel or any other gene therapy or are being considered for treatment with any other gene therapy
- Have adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis
- Do not have any of the following
  - Burkitt lymphoma
  - Active hepatitis B, C, or any uncontrolled infection
  - Grade 2 to 4 graft-versus-host disease
  - Concomitant genetic syndrome with the exception of Down syndrome
  - Received allogeneic cellular therapy, such as donor lymphocyte infusion, within 6 weeks prior to tisagenlecleucel infusion
  - Patient has active central nervous system 3 acute lymphoblastic leukemia (ie, white blood cell count ≥5 cells/μL in cerebrospinal fluid with presence of lymphoblasts).

\(^a\) 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).
CAR-T therapy with tisagenlecleucel intravenous (except as indicated\(^a\)) infusion is considered **medically necessary** for relapsed or refractory\(^b\) patients with aggressive types of non-Hodgkin lymphoma if they meet all of the following criteria:

- Are adults (age ≥18) at the time of infusion
- Histologically confirmed diagnosis of diffuse large B-cell lymphoma, not otherwise specified; or primary mediastinal large B-cell lymphoma\(^a\) or high-grade B-cell lymphoma or diffuse large B-cell lymphoma arising from follicular lymphoma.
- Received adequate prior therapy including all of the following
  - Anti-CD20 monoclonal antibody for CD20-positive tumor
  - Anthracycline-containing chemotherapy regimen
  - For subjects with transformed follicular lymphoma, prior chemotherapy for follicular lymphoma and subsequently have chemorefractory disease after transformation to diffuse large B-cell lymphoma:
    - Have adequate organ and bone marrow function as determined by the treating oncologist/hematologist
    - Have not received prior CD19-directed CAR T-cell therapy treatment or any other gene therapy or are being considered for treatment with any other gene therapy.

**AND**

do not have primary central nervous system lymphoma.

\(^a\) Tisagenlecleucel intravenous infusion is considered **investigational** for the treatment of relapsed or refractory primary mediastinal large B-cell lymphoma.

\(^b\) 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).

CAR-T therapy with axicabtagene ciloleucel infusion is considered **medically necessary** for relapsed or refractory\(^a\) patients with aggressive types of non-Hodgkin lymphoma if they meet all of the following criteria:

- Are adults (age ≥18) at the time of infusion
- Histologically confirmed diagnosis of diffuse large B-cell lymphoma, not otherwise specified; or primary mediastinal large B-cell lymphoma or high-grade B-cell lymphoma or diffuse large B-cell lymphoma arising from follicular lymphoma.
- Received adequate prior therapy including all of the following
  - Anti-CD20 monoclonal antibody for CD20-positive tumor
  - Anthracycline-containing chemotherapy regimen
  - For subjects with transformed follicular lymphoma, prior chemotherapy for follicular lymphoma and subsequently have chemorefractory disease after transformation to diffuse large B-cell lymphoma:
- Have adequate organ and bone marrow function as determined by the treating oncologist/hematologist
- Have not received prior CD19-directed CAR T-cell therapy treatment or any other gene therapy or are being considered for treatment with any other gene therapy.

AND

do not have primary central nervous system lymphoma.

\* 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).

CAR-T therapy is considered **investigational** for all other applications.

**Considerations**

Autologous lymphocytes used as part of chimeric antigen receptor T-cell (CAR-T) therapy may be harvested with an apheresis procedure or may be isolated from resected tumor tissue.

The recommended dosage of tisagenlecleucel for patients with B-cell acute lymphoblastic leukemia who are 50 kg or less is 0.2 to 5.0×10⁶ chimeric antigen receptor-positive viable T cells per kilogram of body weight intravenously; for patients above 50 kg, dose is 0.1 to 2.5×10⁸ total chimeric antigen receptor-positive viable T cells (non-weight-based) intravenously.

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

The recommended target dose of axicabtagene ciloleucel for patients with large B-cell lymphoma is 2×10⁶ CAR-positive viable T cells per kg body weight, with a maximum of 2×10⁸ chimeric antigen receptor-positive viable T cells intravenously.

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 (CRS) and neurologic toxicities (NT) 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 CRS 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.

### Description of Procedure or Service

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

**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 a single-arm prospective trials. The relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The pivotal single-arm trials reported a 81% response rate (measured by complete response or complete remission with incomplete blood count) in heavily pretreated patients. All patients who achieved 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 13.1 months, the median duration of response was not reached. The observed benefits seen with tisagenlecleucel were offset by a high frequency and severity of adverse events. Cytokine release syndrome was observed in more than half (77%) of the patients, and approximately 88% had an adverse event at grade 3 or higher. Long-term follow-up, real-world evidence, and post-marketing studies are required to assess the generalizability of tisagenlecleucel efficacy and safety outside of the clinical trial setting. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are adults with a histologically confirmed diagnosis of aggressive 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 OS, DSS, QOL, and treatment-related mortality and morbidity. The pivotal single-arm trial reported a 52% overall response rate (measured by complete or partial responses) in heavily pretreated patients. After a median follow-up of 14 months, the median duration of response was not reached. The observed benefits were offset by a high frequency and severity of adverse events. Any grade cytokine release syndrome was observed in 58% of the patients, and 63% had an adverse event at grade 3 or higher. Long-term follow-up, real-world evidence, and postmarketing studies 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 OS, DSS, QOL, and treatment-related mortality and morbidity. The pivotal single-arm trial reported a 83% overall response rate (measured by complete or partial remission) in heavily pretreated patients. After a median follow-up of 27.1 months, the median duration of response was 11.1 months. The observed benefits were offset by a high frequency and severity of adverse events. Cytokine release syndrome was observed in more than half of the patients, and 98% had an adverse event at grade 3 or higher. Long-term follow-up and real-world evidence are required to assess the generalizability of axicabtagene ciloleucel efficacy and safety outside of the clinical trial setting. The manufacturer has agreed to a postmarketing requirement observational registry study to collect safety information for patients treated with the marketed product. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Background

**Acute Lymphoblastic Leukemia (ALL)**

B-cell ALL is a malignancy (clonal) of the bone marrow in which the early lymphoid precursors of the white blood cells (called lymphoblasts) proliferate and replace the normal hematopoietic cells of the marrow. This results in overcrowding of the bone marrow, as well as the peripheral organs (particularly the liver, spleen, and lymph nodes) by the lymphoblasts. As a consequence, the leukemic blasts displace the normal hematopoietic bone marrow and cause cytopenias in all three cell lineages (anemia, thrombocytopenia, granulocytopenia). Leukostasis affecting brain and lung may also occur. Death occurs commonly due to severe pancytopenia and resulting infections. Refractory (resistant) disease is defined as those patients who fail to obtain a complete response with induction therapy, ie, failure to eradicate all detectable leukemia cells (<5% blasts) from the bone marrow and blood with subsequent restoration of normal hematopoiesis (>25% marrow cellularity and normal peripheral blood counts). Relapsed disease describes the reappearance of leukemia cells in the bone marrow or peripheral blood after the attainment of complete remission. Minimal residual disease (MRD) refers to the presence of disease in cases deemed to be in complete remission by conventional pathologic analysis. MRD positivity is defined as the presence of 0.01% or more ALL cells and has been shown to be a strongest prognostic factor to predict the risk of relapse and death when measured during and after induction therapy in both newly diagnosed and relapsed ALL. In a meta-analysis of 20 studies of 11249 pediatric ALL, Berry et al (2017) reported a hazard ratio for event-free survival in MRD-negative patients compared with MRD-positive patients of 0.23 (95% confidence interval, 0.18 to 0.28).

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

**Diffuse Large B Cell Lymphoma (DLBCL)**
DLBCL is the most common histologic subtype of non-Hodgkin lymphoma and accounts for approximately 25% of non-Hodgkin lymphoma cases.\(^9\) DLBCL exhibits large heterogeneity in morphologic, genetic, and clinical aspects and multiple clinicopathologic entities are defined by the 2016 World Health Organization classification, which are sufficiently distinct to be considered separate diagnostic categories. Teras et al (2016) has estimated that 27650 new cases of DLBCL were diagnosed in the United States in 2016.\(^10\)

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

**Adoptive Immunotherapy**
Adoptive immunotherapy uses “activated” lymphocytes as a treatment modality. Both nonspecific and specific lymphocyte activation are used therapeutically. The nonspecific, polyclonal proliferation of lymphocytes by cytokines (immune system growth factors), also called autolymphocyte therapy, increases the number of activated lymphocytes.
Initially, this treatment was performed by harvesting peripheral lymphokine-activated killer cells and activating them ex vivo with the T-cell growth factor interleukin-2 (IL-2) and other cytokines. More recent techniques have yielded select populations of cytotoxic T lymphocytes with specific reactivity to tumor antigens. Peripheral lymphocytes are propagated in vitro with antigen-presenting dendritic cells (DC) that have been pulsed with tumor antigens. Alternatively, innate tumor-infiltrating lymphocytes (TIL) from the tumor biopsy are propagated in vitro with IL-2 and anti-CD3 antibody, a T-cell activator. Expansion of TIL for clinical use is labor intensive and requires laboratory expertise. Only a few cancers are infiltrated by T cells in significant numbers; of these, TIL can be expanded in only approximately 50% of cases.\textsuperscript{15}

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

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

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

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

Allogeneic stem cell transplantation following nonmyeloablative conditioning of the recipient (ie, reduced-intensity conditioning) may also be referred to as “adoptive immunotherapy” in the literature. However, reduced-intensity conditioning cell transplantation relies on a donor-vs-malignancy effect of donor lymphocytes. In contrast, the adoptive immunotherapy techniques described in this evidence review enhance autoimmune effects primarily. The use of reduced-intensity conditioning in cell transplantation is discussed for specific cancers in individual policies related to stem cell transplantation.
Chimeric Antigen Receptor T Cell Therapy
Due to difficulties in expanding innate TILs, genetic modification techniques have been harnessed to decorate propagated T cells with engineered chimeric antigen receptors (CARs) that are composed of several functional components: a tumor antigen-targeting single chain variable fragment (scVF) (eg, anti-CD19), a hinge region, a T-cell activation domain (eg, CD3), and one or more costimulatory domains (eg, CD28, 4-1 BB). Viral vector genetic modification approaches (eg, retroviral, lentiviral) have traditionally been used to transfect T cells with CAR genes.17

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

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

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

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

On October 18, 2017, axicabtagene ciloleucel (Yescarta™; Kite Pharma) was approved by the FDA for the treatment of adults with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.
Rationale
This evidence review was created in October 2019 with a search of the MEDLINE database through July 25, 2019.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function¾including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Chimeric antigen receptor T-cell (CAR-T) therapy has been investigated for the treatment of various hematologic malignancies. Novel treatments have been adopted when RCTs show efficacy. In the case of adopted CAR-T therapies, selected studies include only new pivotal trials and RCTs.

Tisagenlecleucel

B-Cell Acute Lymphoblastic Leukemia (ALL)

Clinical Context and Therapy Purpose
The purpose of tisagenlecleucel is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients who are up to 25 years of age with relapsed or refractory B-cell ALL.

The question addressed in this evidence review is: does the use of CAR-T therapy in patients with various hematologic malignancies improve the net health outcome?

The following PICO was used to select literature to inform this review.
Patients
The relevant population of interest are individuals who are up to 25 years of age with relapsed or refractory CD19-positive B-cell ALL. 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. 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).20

Interventions
The therapy being considered is tisagenlecleucel. Therapy with Kymriah (tisagenlecleucel) involves patient apheresis for harvesting of cells to be utilized for autologous T-cell expansion, manufacturing of CAR-positive T-cells, patient completion of a lymphodepleting chemotherapy regimen, and intravenous infusion of Kymriah at a body weight-dependent target dose. For patients who are 50 kg or less, the target dose is 0.2 to 5.0 x 10^6 CAR-positive viable T-cells. For patients who weight more than 50 kg, the target dose is 0.1 to 2.5 x 10^8 CAR-positive viable T-cells. Lymphodepleting chemotherapy with fludarabine (30 mg/m² IV daily for 4 days) and cyclophosphamide (500 mg/m² IV daily for 2 days starting with first dose of fludarabine) is suggested. Kymriah should be infused 2 to 14 days following completion of lymphodepletion regimen.

Kymriah must be administered at a certified healthcare facility. Tocilizumab and emergency equipment must be verified for availability prior to infusion and during the recovery period. Patients must be monitored for signs and symptoms of cytokine release syndrome (CRS) and neurologic toxicities.18

Comparators
Comparators of interest are standard of care as described in guidelines published by the National Comprehensive Cancer Network (NCCN) for pediatric and young adult ALL.20 For Philadelphia chromosome-negative ALL, induction and consolidation chemotherapies are recommended. For Philadelphia chromosome-positive ALL, chemotherapy with tyrosine kinase inhibitor (TKI) therapy is recommended. For high risk disease (age ≥ 10 y and/or white blood cell count >50,000/mm³ or Philadelphia chromosome-positive disease), blinatumomab and hematopoietic stem cell transplantation (HSCT) may be considered. Maintenance therapy post-HSCT with TKI may also be considered.

Outcomes
The general outcomes of interest are overall survival (OS), disease-specific survival (DSS), quality of life (QOL), treatment-related mortality, and treatment-related morbidity. Follow-up at 15 years is of interest for tisagenlecleucel to monitor relevant outcomes.

Treatment options for patients with relapsed or refractory ALL are limited and are associated with poor outcomes and high toxicities. The 2-year overall survival rate
among patients with ALL who relapse after HSCT is 15%. Median objective response rates for blinatumomab in relapsed or refractory ALL are 33%, with a median duration of response of 6 months, and a median OS duration of 7.5 months.\textsuperscript{7,8} Objective or overall response rates are typically calculated as the sum of patients achieving complete response (CR) and CR with incomplete blood count recovery. Partial response is not defined for this disease. Response criteria utilizing conventional morphological features are published by the National Cancer Comprehensive Network (NCCN)\textsuperscript{20}, and are summarized in Table 1.

**Table 1. NCCN Response Criteria for Blood and Marrow\textsuperscript{i}**

<table>
<thead>
<tr>
<th>Response</th>
<th>Criteria</th>
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<tr>
<td>Complete Response (CR)</td>
<td>No circulating blasts or extramedullary disease</td>
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<td></td>
<td>Marrow contains &lt;5% blasts or &lt;1% by flow or molecular testing</td>
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<td>With blood count recovery defined as absolute neutrophil count (ANC) &gt;1000/µL and platelets &gt;100,000/µL</td>
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<td>No recurrence for 4 weeks</td>
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<tr>
<td>Complete Response with Incomplete Blood Count Recovery (CRI)</td>
<td>Meets all criteria for blood count recovery except platelet count and/or ANC</td>
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<td>Progressive Disease (PD)</td>
<td>Increase of least 25% in the absolute number of circulating or marrow blasts, or</td>
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<td></td>
<td>Development of extramedullary disease</td>
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\textsuperscript{i}Table adapted from NCCN guidelines.\textsuperscript{20}

A minimal residual disease (MRD) can also be calculated for patients. MRD refers to the presence of leukemic cells below the limit of detection by conventional morphologic and cytogenetic methods. Patients who achieve a CR by morphologic assessment alone can potentially harbor a significant number of leukemic cells in the bone marrow, and has been shown to contribute to risk of future relapse. Regular MRD monitoring is considered an essential component of patient evaluation. Flow cytometry or PCR methods are recommended for MRD monitoring. 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 pediatric ALL (N = 11,249),
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). Event-free survival in the context of CAR-T therapy is typically defined as the date of infusion to the date of treatment failure (eg, relapse, development of a second neoplasm, or death in remission).

Cytokine release syndrome (CRS) and neurologic toxicity, also known as CAR-T-related encephalopathy syndrome, are two significant CAR-T therapy-mediated adverse events that contribute to treatment-related morbidity and mortality outcomes. CRS manifests with a variety of symptoms, including fever, organ toxicity, hypotension, and hypoxia, and may be life-threatening. CRS is scored Grade 1 to Grade 4 and several criteria are available. The criteria established by Lee and others are commonly used. Consensus guidelines issued by the American Society for Tranplantation and Cellular Therapy (ASTCT) and definitions per the Common Terminology Criteria for Adverse Events issued by the National Cancer Institute (NCI) are also available. These grading systems are summarized in Table 2.

Table 2. CRS Grading Systems

<table>
<thead>
<tr>
<th>Grading System</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee Criteria</td>
<td>Symptoms are not life-threatening (eg, fever, nausea, fatigue, headache, malaise, myalgias) and require symptomatic treatment only.</td>
<td>Symptoms require and respond to moderate intervention: FiO$_2$ &lt;40%, or Hypotension responsive to IV fluids or low-dose of single vasopressor, or Grade 2 organ toxicity is present.</td>
<td>Symptoms require and respond to aggressive intervention: FiO$_2$ $\geq$ 40%, or Hypotension requiring high-dose or multiple vasopressors, or Grade 3 organ toxicity or Grade 4 transaminitis is present.</td>
<td>Symptoms are life-threatening: Ventilator support required, or Grade 4 organ toxicity (excluding transaminitis) is present.</td>
</tr>
<tr>
<td>ASTCT Consensus Criteria</td>
<td>Fever: Temperature $\geq$38°C Hypotension: None Hypoxia: None</td>
<td>Fever: Temperature $\geq$38°C Hypotension: Not requiring vasopressors Hypoxia: Requiring low-flow nasal cannula or blow-by</td>
<td>Fever: Temperature $\geq$38°C Hypotension: Requiring a vasopressor with or without vasopressin Hypoxia: Requiring high-flow nasal</td>
<td>Fever: Temperature $\geq$38°C Hypotension: Requiring multiple vasopressors (excluding vasopressin) Hypoxia: Requiring</td>
</tr>
<tr>
<td>NCI CTCAE Criteria</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>--------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Fever with or without constitutional symptoms</td>
<td>Encephalopathy: Mild symptoms Seizure: Brief partial seizure and no loss of consciousness</td>
<td>Encephalopathy: Moderate symptoms, limiting instrumental ADL Seizure: Brief generalized seizure</td>
<td>Encephalopathy: Severe symptoms, limiting self-care ADL Seizure: New-onset seizures (partial or generalized); multiple seizures despite intervention</td>
<td>Encephalopathy: Life-threatening consequences; urgent intervention indicated Seizure: Life-threatening consequences</td>
</tr>
<tr>
<td>Hypotension responding to fluids; hypoxia responding to &lt;40% O₂</td>
<td></td>
<td></td>
<td>CARTOX-10 Neurologic Assessment Score: 0-2 (severe impairment) Seizure: Partial seizure or nonconvulsive seizure on EEG with response to benzodiazepine</td>
<td>CARTOX-10 Neurologic Assessment Score: 7-9 (mild impairment)</td>
</tr>
<tr>
<td>Hypotension managed with one pressor; hypoxia responding to ≥40% O₂</td>
<td></td>
<td></td>
<td>CARTOX-10 Neurologic Assessment Score: 3-6 (moderate impairment) Seizure: Partial seizure or nonconvulsive seizure on EEG with response to benzodiazepine</td>
<td>CARTOX Consensus Neurologic Assessment Score: Patient in critical condition and/or obtunded and cannot complete assessment tasks Seizure: Generalized seizures or convulsive or nonconvulsive status epilepticus, or new</td>
</tr>
</tbody>
</table>

ASTCT: American Society for Transplantation and Cellular Therapy; CRS: cytokine release syndrome; CTCAE: Common Terminology Criteria for Adverse Events; O₂: oxygen; IV: intravenous; NCI: National Cancer Institute.

1 Adapted from ASTCT\textsuperscript{21} and NCI\textsuperscript{22}.

Criteria for grading of neurological toxicities have been established by both the National Cancer Institute (NCI) and the CARTOX Working Group and are summarized in Table 3.

**Table 3. Neurological Toxicity Grading Systems**

<table>
<thead>
<tr>
<th>Grading System</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARTOX Consensus Criteria</td>
<td>CARTOX-10 Neurologic Assessment Score: 0-2 (severe impairment) Seizure: Partial seizure or nonconvulsive seizure on EEG with response to benzodiazepine</td>
<td>CARTOX-10 Neurologic Assessment Score: 3-6 (moderate impairment) Seizure: Partial seizure or nonconvulsive seizure on EEG with response to benzodiazepine</td>
<td>CARTOX-10 Neurologic Assessment Score: Patient in critical condition and/or obtunded and cannot complete assessment tasks Seizure: Generalized seizures or convulsive or nonconvulsive status epilepticus, or new</td>
<td></td>
</tr>
</tbody>
</table>
Study Selection Criteria
The PICO above was used to select literature to inform this review.

Studies were selected for relevance using the following principles:

1. Reported on the marketed version of the therapy.
2. Patient clinical characteristics were described.
3. Patient selection criteria were described.

Methodologically credible studies were selected using the following principles:

1. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
2. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
3. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
4. Studies with duplicative or overlapping populations were excluded.

Several studies were excluded from the evidence review because they did not identity or use the marketed version of the therapy, did not adequately describe the patient characteristics, or did not adequately describe patient selection criteria.

Pivotal Trials
In the pivotal trial phase 2 single-arm, international, multicenter trial (ELIANA), 92 patients ages 3 to 21 years of screening with CD19-positive relapsed or refractory B-cell ALL were treated with tisagenlecleucel and followed for a median duration of 13.1 months. Trial results were published by Maude et al (2018). Study characteristics and results are summarized in Tables 4-6.

The prespecified primary efficacy endpoint was the proportion of patients who achieved objective remission rate (CR or CR with incomplete blood count recovery [CRi]) as assessed by an independent review committee within three months after tisagenlecleucel infusion. The trial would meet its primary objective if the lower bound of the 2-sided 95% CIs for objective remission rate was greater than 20%. The key secondary outcome was the proportion of patients who achieve the best objective remission rate (CR or CRi with MRD-negative bone marrow) within three months of receiving tisagenlecleucel. Key secondary endpoints were tested sequentially (after primary endpoint was significant) to control for overall type I error.
Of the 107 patients who were screened, 92 met the trial inclusion criteria and of these 75 (81.5%) were infused with tisagenlecleucel. Patients received investigator choice bridging chemotherapy as needed to control their leukemia while waiting for tisagenlecleucel infusion. Patients also received protocol mandated lymphocyte-depleting chemotherapy 2 to 14 days prior to tisagenlecleucel infusion. An overall response rate of 81% was reached for patients who had at least three months of follow-up data available at data cutoff. Median overall survival (OS) was not reached but OS at 6 months post-infusion was 90% and 76% (95% CI: 63 to 86) at 12 months after infusion. Any grade CRS was observed in 77% of patients. Any identified study relevance, design, and conduct limitations are summarized in Tables 7 and 8.

Table 4. Summary of Key Pivotal Trial Characteristics

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Study Type</th>
<th>Country</th>
<th>Dates</th>
<th>Participants</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maude et al (2018); ELIANA</td>
<td>Single-cohort, multicenter, phase 1-2a study</td>
<td>Multiple</td>
<td>2015-2017</td>
<td>Inclusion: Patients aged between 3 and 15 years at diagnosis with at least 5% lymphoblasts in bone marrow at screening. With CD19-positive second or greater bone marrow relapse or primary refractory B-cell acute lymphoblastic leukemia. Exclusion: Prior treatment with anti-CD19 therapy. Total enrolled: 92 Received tisagenlecleucel: 75 Excluded: 17 Product-related issues: 7 Death: 7 Adverse events: 3 Received tisagenlecleucel:</td>
<td>After completing lymphodepleting chemotherapy (96%), tisagenlecleucel was administered as a single intravenous infusion consisting of a median dose of 3.1 x 10⁶ CAR-positive viable T cells per kg of body weight for a median total dose of 1.0 x 10⁸.</td>
</tr>
</tbody>
</table>
ALT: alanine aminotransferase; CI: confidence interval; CNS: central nervous system; CrCl: creatinine clearance; DLBCL: diffuse large B-cell lymphoma; ECOG: Eastern Cooperative Oncology Group; FU: follow-up; HCT: hematopoietic cell transplantation; NR: not reported.

Table 5. Summary of Key Pivotal Trial Efficacy Results

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>ORR\textsuperscript{a}, n (%) (95% CI)</th>
<th>CR, n (%) (95% CI)</th>
<th>CRi, n (%) (95% CI)</th>
<th>Median DOR, mo (95% CI)</th>
<th>EFS, % (95% CI)\textsuperscript{b}</th>
<th>OS, % (95% CI)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maude et al (2018); ELIANA\textsuperscript{24}</td>
<td>N = 75</td>
<td>N = 75</td>
<td>N = 75</td>
<td>N = 61</td>
<td>N = 75</td>
<td>N = 75</td>
</tr>
<tr>
<td>Tisagenlecleucel</td>
<td>61 (81) (71 - 89)</td>
<td>45 (60) (NR)</td>
<td>16 (21) (NR)</td>
<td>NRE (NR)</td>
<td>73 (60 - 82)</td>
<td>90 (81 - 95)</td>
</tr>
</tbody>
</table>

CI: confidence interval; CR: complete response; CRR: complete response rate; DOR: duration of response; EFS: event-free survival; NR: not reported; NRE: not reached; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PR: partial response.

\textsuperscript{a} ORR is a sum of complete response (CR) and complete response with incomplete hematologic recovery (CRi).

\textsuperscript{b} Rates at 6 months post-infusion.

Table 6. Summary of Key Trial Safety Results

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>CRS Grade ≥ 3, n (%)\textsuperscript{1}</th>
<th>Neurological Toxicity Grade ≥ 3, n (%)</th>
<th>Any AE Grade ≥ 3, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maude et al (2018); ELIANA\textsuperscript{24}</td>
<td>N = 75</td>
<td>N = 75</td>
<td>N = 75</td>
</tr>
<tr>
<td>Tisagenlecleucel</td>
<td>35 (46)</td>
<td>10 (13)</td>
<td>66 (88)</td>
</tr>
</tbody>
</table>

AE: adverse event; CRS: cytokine release syndrome.

\textsuperscript{1} CRS was graded according to the Lee criteria.
Table 7. Relevance Limitations

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Population(^a)</th>
<th>Intervention(^b)</th>
<th>Comparator(^c)</th>
<th>Outcomes(^d)</th>
<th>Follow-Up(^e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maude et al (2018); ELIANA(^{24})</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

\(^a\) Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

\(^b\) Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

\(^c\) Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

\(^d\) Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not established and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

\(^e\) Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 8. Study Design and Conduct Limitations

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Allocation(^a)</th>
<th>Blinding(^b)</th>
<th>Selective Reporting(^c)</th>
<th>Data Completeness(^d)</th>
<th>Power(^e)</th>
<th>Statistical(^f)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maude et al (2018); ELIANA(^{24})</td>
<td>1. Allocation is not described.</td>
<td>1. Blinding is not described.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.


\(^b\) Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

\(^c\) Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

\(^d\) Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

\(^e\) Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

\(^f\) Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

**Subsection Summary: B-Cell ALL**

Observed outcomes in single-arm study design cannot be attributed solely to the intervention itself because they could occur as a result of a placebo effect, the natural course of the disease, or confounding by time-varying factors. However, it is unlikely that the 81% response rate (measured by CR or CRi) seen in the pivotal
single-arm trial of tisagenlecleucel in patients with relapsed or refractory ALL could be the result of noninterventional effect. An unbiased estimate of the safety of tisagenlecleucel cannot be ascertained from this evidence base because of the lack of control arm, which makes it difficult to determine whether the observed adverse reactions are a consequence of background disease or the drug itself. However, tisagenlecleucel is a biologic drug and therefore observed adverse reactions that have immunologic basis are likely drug-mediated. The observed benefits seen with tisagenlecleucel were offset by a high frequency and severity of adverse reactions. CRS was observed in more than half (77%) of the patients and approximately 88% had an adverse event at grade 3 or higher. Long-term follow-up, real-world evidence, and post-marketing studies are required to assess the generalizability of tisagenlecleucel efficacy and safety outside of a clinical trial setting.

**Diffuse Large B-Cell Lymphoma**

**Clinical Context and Therapy Purpose**
The purpose of tisagenlecleucel is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients who are adults with specific types of aggressive non-Hodgkin lymphoma (NHL).

The question addressed in this evidence review is: does the use of CAR-T therapy in patients with various hematologic malignancies improve the net health outcome?

The following PICO was used to select literature to inform this review.

**Patients**
The relevant population of interest are individuals who are adults with specific types of relapsed or refractory aggressive NHL. This includes DLBCL not otherwise specified, high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and transformed follicular lymphoma. Relapsed or refractory disease is defined as disease progression after two or more lines of systemic therapy, which may or may not include therapy supported by autologous cell transplant.25

**Interventions**
The therapy being considered is tisagenlecleucel. Therapy with Kymriah (tisagenlecleucel) involves patient apheresis for harvesting of cells to be utilized for autologous T-cell expansion, manufacturing of CAR-positive T-cells, patient completion of a lymphodepleting chemotherapy regimen, and infusion of Kymriah at a target dose of 0.6 to 6.0 x 10^8 CAR-positive viable T cells in one or more infusion bags.

Kymriah must be administered at a certified healthcare facility. Tocilizumab and emergency equipment must be verified for availability prior to infusion and during the recovery period. Patients must be monitored following infusion for signs and symptoms of CRS and neurologic toxicities.18
Comparators
Comparators of interest are standard of care as described in guidelines published by the National Comprehensive Cancer Network (NCCN) for B-cell NHL, which detail standard treatment regimens for DLBCL, high-grade B-cell lymphomas (HGBL), follicular lymphoma (FL), and primary mediastinal large B-cell lymphoma (PMBL).25

For DLBCL, initial treatment typically includes a patient-specific regimen of RCHOP chemotherapy (ie, rituximab, cyclophosphamide, doxorubicin HCl, vincristine sulfate, and prednisone) with or without radiotherapy at the involved site. For disease that does not respond to first-line treatment, separate alternative and/or high-dose chemotherapy regimens are recommended for those that intend to proceed to autologous stem cell transplant (eg, DHAP, DHAX, ESHAP, GDP, GemOx, ICE, MINE) and those who are non-candidates for transplant (eg, bendamustine +/- rituximab, CEPP, CEOP, DA-EPOCH +/- rituximab, ibrutinib, rituximab, and others).

For PMBL, initial treatment typically involves one of several chemotherapy regimens (eg, EPOCH-R, RCHOP + ICE) with or without radiotherapy. For patients who do not respond to first-line treatment, pembrolizumab or transplant-dependent second-line chemotherapy regimens described previously may be used.

For HGBL, the standard of care has not been established. Clinical trials are recommended. For HGBL with double-hit (ie, translocation of MYC and BCL2 genes) or triple-hit (ie, translocation of MYC, BCL2, and BCL6 genes) genotypes, the DA-EPOCH-R chemotherapy regimen has been used at NCCN member institutions. For HGBL not otherwise specified, consolidative radiotherapy should be considered for early-stage disease. The RCHOP and DA-EPOCH-R chemotherapy regimens have been used at NCCN member institutions.

For FL, initial treatment may include radiotherapy at the involved site, anti-CD20 monoclonal antibody with or without chemotherapy, or anti-CD20 monoclonal antibody and radiotherapy with or without chemotherapy. Standard chemotherapy regimens for FL include bendamustine + obinutuzumab or rituximab, CHOP, CVP, lenalidomide + rituximab, or rituximab. Additional second-line chemotherapies include CHOP with obinutuzumab or rituximab, CVP with obinutuzumab or rituxumab, and lenalidomide with or without rituximab. High-dose chemotherapy with allogeneic hematopoietic cell transplant may also be considered, particularly in cases where histological transformation to DLBCL has occurred.

Outcomes
The general outcomes of interest are OS, DSS, QOL, treatment-related mortality, and treatment-related morbidity. To serve as a reference point for a subsequent review of the intervention and to inform minimum follow-up durations, outcomes observed with standard of care are briefly summarized.
Outcomes for patients with relapsed and refractory DLBCL are poor, as determined by a retrospective analysis of the SCHOLAR-1 study by Crump et al (2017) which pooled data from two, phase 3 clinical trials and 2 observational cohorts (N = 636). The objective response rate to the next line of therapy was 26%, with only 7% achieving a complete response. Median overall survival was 6.3 months and 2-year survival was 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. HGBL also often presents with a poor prognosis, due to bone marrow and central nervous system involvement and high International Prognostic Index (IPI) scores. IPI scores are calculated for a range of 0 to 5, with 1 point added toward the total score for each criteria met below:

- Age > 60 years
- Serum LDH > normal
- Performance status 2-4
- Stage III or IV disease
- Extranasal involvement > 1 site

Risk groups are stratified as follows:

- Low (0-1)
- Low-intermediate (2)
- High-intermediate (3)
- High (4-5)

Treatment response is characterized according to the Lugano criteria, described below in Table 9. The objective response (OR) is typically reported as the sum of complete (CR) and partial responses (PR). Though not standardized, follow-up for individuals who are adults with specific types of aggressive NHL would typically occur in the months after starting treatment. SCHOLAR-1 data suggests that survival outcomes should be followed for a minimum of 1-2 years.

**Table 9. Lugano Response Criteria for NHL**

<table>
<thead>
<tr>
<th>Response</th>
<th>Site</th>
<th>PET-CT (Metabolic Response)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (CR)</td>
<td>Lymph nodes and extralymphatic sites</td>
<td>Score 1, 2, 3 with or without a residual mass on a 5 point scale²</td>
</tr>
<tr>
<td></td>
<td>Non-measured lesion</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Organ enlargement</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>New lesions</td>
<td>Bone marrow</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td><strong>Partial Response (PR)</strong></td>
<td>None</td>
<td>No evidence of disease in marrow</td>
</tr>
<tr>
<td>Lymph nodes and extralymphatic sites</td>
<td>Score 4 or 5 with reduced uptake compared to baseline and no new progressive lesions</td>
<td></td>
</tr>
<tr>
<td>Non-measured lesion</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Organ enlargement</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>New lesions</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Residual uptake higher than uptake in normal marrow but reduced compared with baseline</td>
<td></td>
</tr>
<tr>
<td><strong>Stable Disease or No Response</strong></td>
<td>Score 4 or 5 with no significant change in uptake from baseline at interim or end of treatment; no new or progressive lesions.</td>
<td></td>
</tr>
<tr>
<td>Lymph nodes and extralymphatic sites</td>
<td>Score 4 or 5 with no significant change in uptake from baseline at interim or end of treatment; no new or progressive lesions.</td>
<td></td>
</tr>
<tr>
<td>Non-measured lesion</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Organ enlargement</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>New lesions</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Bone marrow</td>
<td>No change from baseline</td>
<td></td>
</tr>
<tr>
<td><strong>Progressive Disease</strong></td>
<td>Score 4 or 5 with an increase in intensity of uptake from baseline and/or new foci consistent with lymphoma</td>
<td></td>
</tr>
<tr>
<td>Lymph nodes and extralymphatic sites</td>
<td>Score 4 or 5 with an increase in intensity of uptake from baseline and/or new foci consistent with lymphoma</td>
<td></td>
</tr>
<tr>
<td>Non-measured lesion</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>New lesions</td>
<td>New foci consistent with lymphoma</td>
<td></td>
</tr>
<tr>
<td>Bone marrow</td>
<td>New or recurrent foci</td>
<td></td>
</tr>
</tbody>
</table>
Achievement of complete remission and durability of response is associated with improved health outcomes for patients with aggressive NHL, a disease where many patients relapse or are refractory to existing interventions. Progression-free survival (PFS) is the context of CAR-T therapy is typically defined as the date of CAR T-cell infusion to date of disease progression or death by any cause. Duration of response is typically defined as the date of first objective response (partial or complete) to date of disease progression or death by any cause. \(^2\)

Cytokine release syndrome (CRS) and neurologic toxicity, also known as CAR-T-related encephalopathy syndrome, are two significant CAR-T therapy-mediated adverse events that contribute to treatment-related morbidity and mortality outcomes. CRS manifests with a variety of symptoms, including fever, organ toxicity, hypotension, and hypoxia, and may be life-threatening. CRS is scored Grade 1 to Grade 4 and several criteria are available. The criteria established by Lee and others are commonly used. Consensus guidelines issued by the American Society for Transplantation and Cellular Therapy (ASTCT)\(^2\) and definitions per the Common Terminology Criteria for Adverse Events issued by the National Cancer Institute (NCI)\(^2\) are also available. These grading systems were summarized previously in Table 2. Criteria for grading of neurological toxicities have been established by both the National Cancer Institute (NCI) and the CARTOX Working Group\(^2\) and were summarized previously in Table 3.

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2. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
3. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
4. Studies with duplicative or overlapping populations were excluded.
Several studies were excluded from the evidence review because they did not identify or use the marketed version of the therapy, did not adequately describe the patient characteristics, or did not adequately describe patient selection criteria.23

**Pivotal Trials**
The pivotal trial phase 2 single-arm, multicenter trial (JULIET; NCT02445248) enrolled 165 patients with relapsed or refractory DLBCL. Data were obtained from Schuster et al (2019) containing published outcomes at a median data cutoff of 14 months.28 Tables 10 and 11 summarize study characteristics and results.

Of the 165 patients enrolled in the study, 95 patients were retrospectively identified and analyzed for the major efficacy outcome. Table 10 summarizes the reasons for exclusion of patients. The prespecified primary efficacy endpoint was ORR based on Lugano criteria25, as assessed by an independent review committee and duration of response. Patients were heavily pretreated with a median of 3 prior therapies (range, 1-6), 56% had refractory disease and 44% relapsed after their last therapy. Response durations were longer in patients who achieved CR, as compared with patients with the best response of partial response. The response was consistent across subgroups (<65 or ≥65 years, sex, ≤2 or >2 antineoplastic therapies, nongerminal or germinal cancer, rearranged MYC/BCL2/BCL6 or not) (data not shown).

Table 12 summarizes safety data assessed for 111 patients treated with tisagenlecleucel. Any identified study relevance, design, and conduct limitations are summarized in Tables 13 and 14.

### Table 10. Summary of Key Pivotal Trial Characteristics

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Study Type</th>
<th>Country</th>
<th>Dates</th>
<th>Participants</th>
<th>Treatment</th>
<th>Follow-Up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schuster et al (2019); JULIET28</td>
<td>Single-group, open-label, multicenter, international phase 2a study</td>
<td>Multiple</td>
<td>2015-2017</td>
<td>Inclusion: Patients with relapsed or refractory DLBCL, who received ≥2 lines of chemotherapy, including rituximab and anthracycline, or relapsed following HCT Exclusion: Active CNS malignancy, prior allogeneic HCT, ECOG</td>
<td>Two to 11 d after completing lymphodepleting chemotherapy, tisagenlecleucel was administered as a single intravenous infusion consisting of a median dose of 3.0 x 10⁸ CAR-positive viable T cells.</td>
<td>14 (Range: 0.1 - 26.0)</td>
</tr>
</tbody>
</table>
Performance Status ≥2, CrCl <60 L/min, ALT >5 times normal, cardiac ejection fraction <45%, or absolute lymphocyte concentration <300/μL
Total N=165
Receiving US tisagenlecleucel: 95
Discontinued study before infusion: 50
Awaiting infusion at data cutoff: 4
Received an infusion <3 mo before data cutoff: 2
Included and analyzed: 93

ALT: alanine aminotransferase; CI: confidence interval; CNS: central nervous system; CrCl: creatinine clearance; DLBCL: diffuse large B-cell lymphoma; ECOG: Eastern Cooperative Oncology Group; FU: follow-up; HCT: hematopoietic cell transplantation; NR: not reported.

Table 11. Summary of Key Pivotal Trial Efficacy Results

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>ORR*, n (%) (95% CI)</th>
<th>CR, n (%) (95% CI)</th>
<th>PR, n (%) (95% CI)</th>
<th>Median DOR, mo (95% CI)</th>
<th>Estimated rate of PFS at 12 mo for those achieving OR, %</th>
<th>Median OS, mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schuster et al (2019); JULIET²⁸.</td>
<td>N = 93</td>
<td>N = 93</td>
<td>N = 93</td>
<td>N = 48</td>
<td>N = 48</td>
<td>N = 93</td>
</tr>
<tr>
<td>Tisagenlecleucel</td>
<td>48 (52) (41 - 62)</td>
<td>37 (40) (NR)</td>
<td>11 (12) (NR)</td>
<td>NRE (10 - NE)b</td>
<td>83</td>
<td>12 (7 - NE)</td>
</tr>
</tbody>
</table>

BOR: best overall response; CI: confidence interval; CR: complete response; CRR: complete response rate; DOR: duration of response; NR: not reported; NRE: not reached; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PR: partial response.

* ORR is a sum of complete (CR) and partial (PR) responses.

b Among all responders, DOR measured from date of first objective response to date of progression or death from relapse.
Table 12. Summary of Key Trial Adverse Events

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>CRS Grade ≥ 3, n (%)¹</th>
<th>Neurological Toxicity Grade ≥ 3, n (%)</th>
<th>Any AE Grade ≥ 3, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schuster et al (2019); JULIET 28</td>
<td>N = 111</td>
<td>N = 111</td>
<td>N = 111</td>
</tr>
<tr>
<td>Tisagenlecleucel</td>
<td>36 (32)</td>
<td>13 (12)</td>
<td>70 (63)</td>
</tr>
</tbody>
</table>

AE: adverse event; CRS: cytokine release syndrome.
¹ CRS was graded according to the Lee criteria.

Table 13. Relevance Limitations

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Populationa</th>
<th>Interventionb</th>
<th>Comparatorc</th>
<th>Outcomesd</th>
<th>Follow-Up²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schuster et al (2019); JULIET 28</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not established and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

² Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 14. Study Design and Conduct Limitations

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Allocationa</th>
<th>Blindingb</th>
<th>Selective Reportingc</th>
<th>Data Completenessd</th>
<th>Powere</th>
<th>Statisticalf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schuster et al (2019); JULIET 28</td>
<td>1. Allocation is not described.</td>
<td>1. Blinding is not described.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

Subsection Summary: Diffuse Large B-Cell Lymphoma
Observed outcomes in single-arm study design cannot be attributed solely to the intervention itself because they could occur as a result of a placebo effect, the natural course of the disease, or confounding by time-varying factors. However, it is unlikely the high response rate (measured by complete and partial responses) seen in the pivotal trial of tisagenlecleucel could be the result of a noninterventional effect. An unbiased estimate of the safety of these chimeric antigen receptor T- cells cannot be ascertained from this evidence base because of the lack of control arm, which makes it difficult to determine whether the observed adverse reactions are a consequence of background disease or the drug itself. However, tisagenlecleucel is a biologic drug and therefore observed adverse reactions that have immunologic basis are likely drug-mediated. The observed benefits seen with tisagenlecleucel were offset by a high frequency and severity of adverse reactions. Any grade CRS was observed in 58% of treated patients in the pivotal trial. Long-term follow-up, real-world evidence, and post-marketing studies are required to assess the generalizability of efficacy and safety of tisagenlecleucel outside of a clinical trial setting.

Axicabtagene Ciloleucel

Clinical Context and Therapy Purpose
The purpose of axicabtagene ciloleucel is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients who are adults with specific types of aggressive NHL.

The question addressed in this evidence review is: does the use of CAR-T therapy in patients with various hematologic malignancies improve the net health outcome?

The following PICO was used to select literature to inform this review.

Patients
The relevant population of interest are individuals who are adults with specific types of relapsed or refractory aggressive NHL. This includes DLBCL not otherwise specified, high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and transformed follicular lymphoma. Relapsed or refractory disease is
defined as disease progression after two or more lines of systemic therapy, which may or may not include therapy supported by autologous cell transplant.  

**Interventions**
The therapy being considered is axicabtagene ciloleucel. Therapy with Yescarta (axicabtagene ciloleucel) involves patient apheresis for harvesting of cells to be utilized for autologous T-cell expansion, manufacturing of CAR-positive T-cells, patient completion of a lymphodepleting chemotherapy regimen, and infusion of Yescarta at a target dose of $2 \times 10^6$ CAR-positive viable T cells/kg body weight, with a maximum of up to $2 \times 10^8$ CAR-positive viable T-cells permitted.

Yescarta must be administered at a certified healthcare facility. Tocilizumab and emergency equipment must be verified for availability prior to infusion and during the recovery period. Patients must be monitored at least daily for 7 days at the facility following infusion for signs and symptoms of CRS and neurologic toxicities.

**Comparators**
Comparators of interest are standard of care as described in guidelines published by the National Comprehensive Cancer Network (NCCN) for B-cell NHL, which detail standard treatment regimens for DLBCL, high-grade B-cell lymphomas (HGBL), follicular lymphoma (FL), and primary mediastinal large B-cell lymphoma (PMBL). For DLBCL, initial treatment typically includes a patient-specific regimen of RCHOP chemotherapy (ie, rituximab, cyclophosphamide, doxorubicin HCl, vincristine sulfate, and prednisone) with or without radiotherapy at the involved site. For disease that does not respond to first-line treatment, separate alternative and/or high-dose chemotherapy regimens are recommended for those that intend to proceed to autologous stem cell transplant (eg, DHAP, DHAX, ESHAP, GDP, GemOx, ICE, MINE) and those who are non-candidates for transplant (eg, bendamustine +/- rituximab, CEPP, CEOP, DA-EPOCH +/- rituximab, ibrutinib, rituximab, and others).

For PMBL, initial treatment typically involves one of several chemotherapy regimens (eg, EPOCH-R, RCHOP + ICE) with or without radiotherapy. For patients who do not respond to first-line treatment, pembrolizumab or transplant-dependent second-line chemotherapy regimens described previously may be used.

For HGBL, the standard of care has not been established. Clinical trials are recommended. For HGBL with double-hit (ie, translocation of MYC and BCL2 genes) or triple-hit (ie, translocation of MYC, BCL2, and BCL6 genes) genotypes, the DA-EPOCH-R chemotherapy regimen has been used at NCCN member institutions. For HGBL not otherwise specified, consolidative radiotherapy should be considered for early-stage disease. The RCHOP and DA-EPOCH-R chemotherapy regimens have been used at NCCN member institutions.
For FL, initial treatment may include radiotherapy at the involved site, anti-CD20 monoclonal antibody with or without chemotherapy, or anti-CD20 monoclonal antibody and radiotherapy with or without chemotherapy. Standard chemotherapy regimens for FL include bendamustine + obinutuzumab or rituximab, CHOP, CVP, lenalidomide + rituximab, or rituximab. Additional second-line chemotherapies include CHOP with obinutuzumab or rituximab, CVP with obinutuzumab or rituximab, and lenalidomide with or without rituximab. High-dose chemotherapy with allogeneic hematopoietic cell transplant may also be considered, particularly in cases where histological transformation to DLBCL has occurred.

Outcomes
The general outcomes of interest are OS, DSS, QOL, treatment-related mortality, and treatment-related morbidity. To serve as a reference point for a subsequent review of the intervention and to inform minimum follow-up durations, outcomes observed with standard of care are briefly summarized.

Outcomes for patients with relapsed and refractory DLBCL are poor, as determined by a retrospective analysis of the SCHOLAR-1 study by Crump et al (2017) which pooled data from two, phase 3 clinical trials and 2 observational cohorts (N = 636). The objective response rate to the next line of therapy was 26%, with only 7% achieving a complete response. Median overall survival was 6.3 months and 2-year survival was 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. HGBL also often presents with a poor prognosis, due to bone marrow and central nervous system involvement and high International Prognostic Index (IPI) scores. IPI scores are calculated for a range of 0 to 5, with 1 point added toward the total score for each criteria met below:

- Age > 60 years
- Serum LDH > normal
- Performance status 2-4
- Stage III or IV disease
- Extranodal involvement > 1 site

Risk groups are stratified as follows:

- Low (0-1)
- Low-intermediate (2)
- High-intermediate (3)
- High (4-5)

Treatment response is characterized according to the Lugano criteria, described previously in Table 9. The objective response (OR) is typically reported as the sum of complete (CR) and partial responses (PR). Though not standardized, follow-up for individuals who are adults with specific types of aggressive NHL would typically occur in the months after starting treatment. SCHOLAR-1 data suggests that survival outcomes should be followed for a minimum of 1-2 years.
Achievement of complete remission and durability of response is associated with improved health outcomes for patients with aggressive NHL, a disease where many patients relapse or are refractory to existing interventions. Progression-free survival (PFS) is the context of CAR-T therapy is typically defined as the date of CAR T-cell infusion to date of disease progression or death by any cause. Duration of response is typically defined as the date of first objective response (partial or complete) to date of disease progression or death by any cause.

Cytokine release syndrome (CRS) and neurologic toxicity, also known as CAR-T-related encephalopathy syndrome, are two significant CAR-T therapy-mediated adverse events that contribute to treatment-related morbidity and mortality outcomes. CRS manifests with a variety of symptoms, including fever, organ toxicity, hypotension, and hypoxia, and may be life-threatening. CRS is scored Grade 1 to Grade 4 and several criteria are available. The criteria established by Lee and others are commonly used. Consensus guidelines issued by the American Society for Transplantation and Cellular Therapy (ASTCT) and definitions per the Common Terminology Criteria for Adverse Events issued by the National Cancer Institute (NCI) are also available. These grading systems were summarized previously in Table 2.

Criteria for grading of neurological toxicities have been established by both the National Cancer Institute (NCI) and the CARTOX Working Group, and are summarized previously in Table 3.

**Study Selection Criteria**
The PICO above was used to select literature to inform this review.

Studies were selected for relevance using the following principles:

1. Reported on the marketed version of the therapy.
2. Patient clinical characteristics were described.
3. Patient selection criteria were described.

Methodologically credible studies were selected using the following principles:

1. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
2. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
3. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
4. Studies with duplicative or overlapping populations were excluded.

Several studies were excluded from the evidence review because they did not identity or use the marketed version of the therapy, did not adequately describe the patient characteristics, or did not adequately describe patient selection criteria.
Pivotal Trial
The approval of axicabtagene ciloleucel was based on the results of an open-label, multicenter phase 1-2 study called ZUMA-1, which reported response rates and duration of response demonstrated in the phase 2 portion of the study. Data were obtained from the FDA documents and the approved label and a recent publication by Locke and coworkers with 2-year follow-up results.18,30,31,32 Adults with aggressive B-cell NHL that was primary refractory, refractory to a second or greater line of therapy, or relapsed within one year after autologous HCT were enrolled in the study. Patients with prior allogeneic HCT, any history of central nervous system lymphoma, Eastern Cooperative Oncology Group Performance Status score of 2 or greater, absolute lymphocyte count less than 100/μL, creatinine clearance less than 60 mL/min, hepatic transaminases more than 2.5 times the upper limit of normal, cardiac ejection fraction less than 50%, or active serious infection were excluded. Most patients (74%) had de novo DLBCL and 32% had double- or triple-hit lymphoma. The median age was 58, with 24% being aged 65 years or older; the median number of prior therapies was 3; 77% had refractory disease to a second or greater line of therapy, and 21% had relapsed within 1 year after autologous hematopoietic cell transplantation.

All patients received a lymphodepleting regimen consisted of cyclophosphamide and fludarabine prior to infusion of axicabtagene ciloleucel. Of the 111 patients who underwent leukapheresis, 101 received the infusion (9 were not treated due to progressive disease or serious adverse reactions following leukapheresis and there was a manufacturing failure in 1 patient). The study protocol mandated hospitalization of patients for infusion and seven days after infusion. Bridging chemotherapy between leukapheresis and lymphodepleting chemotherapy was not permitted. The median time from leukapheresis to product delivery was 17 days (range, 14-51 days). The primary endpoint was objective response rate based on a modified intention-to-treat population, which was defined as all patients treated with at least $1.0 \times 10^6$ chimeric antigen receptor-positive T cells per kilogram. Tables 13-15 summarizes the trial characteristics and results. Tables 16-17 summarize any identified study relevance, design, and conduct limitations.

Table 13. Summary of Key Trial Characteristics

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Study Type</th>
<th>Country</th>
<th>Dates</th>
<th>Participants</th>
<th>Treatment</th>
<th>Follow-Up, mo (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locke et al (2019); ZUMA-1</td>
<td>Single-arm, multicenter, prospective, phase 1-2</td>
<td>US; Israel</td>
<td>2015-2018</td>
<td>Adult Individuals with histologically confirmed aggressive B-cell NHL (eg, diffuse large</td>
<td>Axicabtagene ciloleucel (N = 108) on day 0 with target dose of 2 x 106 CAR T cells/kg after conditioning chemotherapy</td>
<td>27.1 (25.7-28.8)</td>
</tr>
</tbody>
</table>
B-cell lymphoma not otherwise specified, high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, transformed follicular lymphoma) that was primary refractory, refractory to second or greater line of therapy, or relapsed within one year of autologous HCT. Patients with prior allogeneic HCT, any history of CNS lymphoma, ECOG performance status ≥2, absolute lymphocyte count < 100/μL, creatinine clearance < 60 mL/min, hepatic transaminases > 2.5X ULN, cardiac ejection fraction < 50%, or active serious infection were excluded.

| Adapted from | Single-arm, multicenter, US; Israel | 2015-2017 | Same as above | Same as above | 7.9 (NR) | Chimeric Antigen Receptor Therapy for Hematologic Malignancies 8.01.63 | fludarabine (30 mg/m2) and cyclophosphamide (500 mg/m2) on days -5, -4, and -3. |
**Table 14. Summary of Key Trial Efficacy Results**

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Primary Outcome, Median (%) (95% CI)</th>
<th>OS, Median (95% CI)</th>
<th>Median PFS, mo (95% CI)</th>
<th>Median Duration of Response, mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR CR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Locke et al (2019); ZUMA-1</td>
<td>N = 101</td>
<td>N = 101</td>
<td>N = 101</td>
<td>N = 101</td>
</tr>
<tr>
<td>2-yr Follow-Up</td>
<td>84 (83%) (NR)</td>
<td>59 (58%) (NR)</td>
<td>NRE (12.8 - NE)</td>
<td>5.9 (3.3 - 15.0)</td>
</tr>
<tr>
<td>Adapted from Kite Pharma (2017); ZUMA-1</td>
<td>N = 101</td>
<td>N = 101</td>
<td>N = 101</td>
<td>N = 101</td>
</tr>
<tr>
<td>Initial Follow-Up</td>
<td>73 (72) (62-81)</td>
<td>52 (51) (41-62)</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

CI: confidence interval; CR: complete response; NR: not reported; NRE: not reached; OR: objective response.

1 The objective response (OR) is the sum of complete (CR) and partial (PR) responses and were graded according to Lugano PET criteria.

**Table 15. Summary of Key Trial Safety Results**

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>CRS Grade ≥ 3, n (%)</th>
<th>Neurological Toxicity Grade ≥ 3, n (%)</th>
<th>Any AE Grade ≥ 3, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locke et al (2019); ZUMA-1</td>
<td>N = 101</td>
<td>N = 108</td>
<td>N = 108</td>
</tr>
<tr>
<td>2-yr Follow-Up</td>
<td>12 (11)</td>
<td>35 (32)</td>
<td>106 (98)</td>
</tr>
<tr>
<td>Adapted from Kite Pharma (2017); ZUMA-1</td>
<td>N = 108</td>
<td>N = 108</td>
<td>N = 108</td>
</tr>
</tbody>
</table>
AE: adverse event; CRS: cytokine release syndrome.

CRS was graded according to the Lee criteria.

Table 16. Relevance Limitations

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locke et al (2019); ZUMA-1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not established and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 17. Study Design and Conduct Limitations

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Allocation</th>
<th>Blinding</th>
<th>Selective Reporting</th>
<th>Data Completeness</th>
<th>Power</th>
<th>Statistical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locke et al (2019); ZUMA-1</td>
<td>1. Allocation is not described.</td>
<td>1. Blinding is not described.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Subsection Summary: Axicabtagene Ciloleucel

Observed outcomes in single-arm study design cannot be attributed solely to the intervention itself because they could occur as a result of a placebo effect, the natural course of the disease, or confounding by time-varying factors. However, it is unlikely the high response rate (measured by complete plus partial response) seen in the pivotal trials of axicabtagene ciloleucel could be the result of a noninterventional effect. An unbiased estimate of the safety of this CAR-T therapy cannot be ascertained from this evidence base because of the lack of control arm, which makes it difficult to determine whether the observed adverse reactions are a consequence of background disease or the drug itself. However, axicabtagene ciloleucel is a biologic drug and therefore observed adverse reactions that have immunologic basis are likely drug-mediated. The observed benefits seen with axicabtagene ciloleucel were offset by a high frequency and severity of adverse reactions. Any grade CRS was observed in more than half of the patients in the pivotal trials and 98% of patients had an adverse event at grade 3 or higher. Post-marketing studies and real-world evidence are required to assess the generalizability of efficacy and safety of axicabtagene ciloleucel outside of a clinical trial setting.

Summary of Evidence

Tisagenlecleucel

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

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

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

**SUPPLEMENTAL INFORMATION**

**Practice Guidelines and Position Statements**

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

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

- Philadelphia chromosome-positive patients 26 years or less in age with refractory disease or 2 or more relapses and failure of 2 tyrosine kinase inhibitors.
- Philadelphia chromosome-negative patients 26 years or less in age with refractory disease or 2 or more relapses.
Current Network guidelines for B-cell non-Hodgkin lymphoma (v.4.2019) recommend (category 2A) axicabtagene ciloleucel or tisagenlecleucel as a treatment option for:

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

Footnotes

Footnotes

\(^i\) Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Pediatric Acute Lymphoblastic Leukemia V.1.2020 and B-Cell Lymphomas V.4.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed September 2, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org.

\(^ii\) NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

1. Patient has:
   - relapsed or refractory cancer; and
   - is not currently experiencing any comorbidity that would otherwise preclude benefit.
2. The hospital has:
   - a Cellular Therapy Program consisting of an integrated medical team; and
   - a designated care area; and
   - written guidelines for the administration of chimeric antigen receptor T-cell therapy for patient communication, monitoring, and transfer to an intensive care unit.
3. The treatment meets the criteria in section a or b, below:
   - The treatment is an FDA-approved biological, indicated for use in a hospital setting.
   - The treatment is an FDA-approved biological, indicated for use identified in the National Comprehensive Cancer Network Drugs and Biologics Compendium.
CMS proposes to non-cover the use of CAR-expressing T-cells for any treatment that does not involve an FDA-approved biological product.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 18.

**Table 18. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tisagenlecleucel</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02445248a</td>
<td>A Phase II, Single Arm, Multicenter Trial to Determine the Efficacy and Safety of CTL019 in Adult Patients With Relapsed or Refractory Diffuse Large B-cell Lymphoma</td>
<td>116</td>
<td>Feb 2023</td>
</tr>
<tr>
<td>NCT02445222a</td>
<td>Long Term Follow-Up of Patients Exposed to Lentiviral-Based CD19 Directed CAR T-Cell Therapy</td>
<td>620</td>
<td>May 2035</td>
</tr>
<tr>
<td>NCT03876769a</td>
<td>A Phase II Trial of Tisagenlecleucel in First-Line High-Risk (HR) Pediatric and Young Adult Patients with B-cell Acute Lymphoblastic Leukemia (B-ALL) Who Are Minimal Residual Disease Positive at the End of Consolidation Therapy</td>
<td>140</td>
<td>Aug 2027</td>
</tr>
<tr>
<td><strong>Axicabtagene ciloleucel</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02601313a</td>
<td>A Phase 2 Multicenter Study Evaluating Subjects with Relapse/Refractory Mantle Cell Lymphoma (ZUMA-2)</td>
<td>130</td>
<td>Jan 2035</td>
</tr>
<tr>
<td>NCT02614066a</td>
<td>A Study Evaluating KTE-C19 in Adult Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (r/r ALL) (ZUMA-3) (ZUMA-3)</td>
<td>100</td>
<td>Mar 2034</td>
</tr>
<tr>
<td>NCT02625480a</td>
<td>A Multi-Center Study Evaluating KTE-C19 in Pediatric and Adolescent Subjects With</td>
<td>100</td>
<td>Jan 2036</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>
<td>--------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>NCT03105336a</td>
<td>A Phase 2 Multicenter Study of Axicabtagene Ciloleucel in Subjects With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma (ZUMA-5)</td>
<td>160</td>
<td>Mar 2035</td>
</tr>
<tr>
<td>NCT02228096a</td>
<td>A Phase II, Single Arm, Multicenter Trial to Determine the Efficacy and Safety of CTL019 in Pediatric Patients With Relapsed and Refractory B-cell Acute Lymphoblastic Leukemia</td>
<td>64</td>
<td>May 2019</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

REFERENCES


29. NA


Billing Coding/Physician Documentation Information

0537T 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

0538T Chimeric antigen receptor T-cell (CAR-T) therapy; preparation of blood-derived T lymphocytes for transportation (eg, cryopreservation, storage)

0539T Chimeric antigen receptor T-cell (CAR-T) therapy; receipt and preparation of CAR-T cells for administration

0540T Chimeric antigen receptor T-cell (CAR-T) therapy; CAR-T cell administration, autologous

Q2041 Axicabtagene ciloleucel, up to 200 million autologous anti-cd19 car positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose

Q2042 Tisagenlecleucel, up to 600 million car-positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose

ICD-10 Codes

C82.00- C85.99 Non-Hodgkin Lymphoma range

C91.00- C91.02 Acute lymphoblastic leukemia code range

Z80.6 Family history of leukemia

Z80.7 Family history of other malignant neoplasms of lymphoid, hematopoietic and related tissues

Z85.72 Personal history of non-Hodgkin lymphomas

Additional Policy Key Words

Car T, CAR-T, T-cell

Policy Implementation/Update Information

12/1/19 New policy created from Policy 8.01.01 (Adoptive Immunotherapy). FDA approved tisagenlecleucel and axicabtagene ciloleucel therapies were moved from 8.01.01 to create a new standalone policy 8.01.63 (Chimeric Antigen Receptor Therapy for Hematologic Malignancies)
State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.