Adoptive Immunotherapy

DISCLAIMER

Our medical policies are designed for informational purposes only and are not an authorization, explanation of benefits or a contract. Receipt of benefits is subject to satisfaction of all terms and conditions of the coverage. Medical technology is constantly changing, and we reserve the right to review and update our policies periodically.

POLICY

Tisagenlecleucel intravenous infusion is considered medically necessary for relapsed\(^a\) or refractory\(^b\) patients 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).

Axicabtagene ciloleucel or tisagenlecleucel intravenous (except as indicated\(^a\)) infusion is considered medically necessary for relapsed or refractory\(^b\) patients if they meet all of the following criteria:
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- 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.

°Tisagenlecleucel intravenous infusion is considered investigational for the treatment of relapsed or refractory primary mediastinal large B-cell 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).

Other applications of adoptive immunotherapy are considered investigational.

**POLICY GUIDELINES**

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

The recommended dosage of tisagenlecleucel for patients with B-cell acute lymphoblastic leukemia who are 50 kg or less is 0.2 to 5.0×10⁶ 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 6.0×10⁶ chimeric antigen receptor–positive viable T cells intravenously.

The recommended target dose of axicabtagene ciloleucel for patients with large B-cell lymphoma is 2×10⁸ CAR-positive viable T cells per kg body weight, with a maximum of 2×10⁹ chimeric antigen receptor–positive viable T cells intravenously.

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

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

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

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

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

**BENEFIT APPLICATION**

**BLUECARD/NATIONAL ACCOUNT ISSUES**
Adoptive immunotherapy is a specialized service that may require an out-of-network referral.

Some Plans may participate in voluntary programs offering coverage for patients participating in National Institutes of Health–approved clinical trials of cancer chemotherapies, including adoptive immunotherapy.

**BACKGROUND**

**ACUTE LYMPHOBlastic LEUKEMIA**
Acute lymphoblastic leukemia (ALL) is a malignancy (clonal) of the bone marrow in which the early lymphoid precursors of the white blood cells (called lymphoblasts) proliferate and replace the normal hematopoietic cells of the marrow. This results in overcrowding of the bone marrow, as well as the peripheral organs (particularly the liver, spleen, and lymph nodes) by the lymphoblasts. As a consequence, the leukemic blasts displace the normal hematopoietic bone marrow and cause cytopenias in all 3 cell lineages (anemia, thrombocytopenia, granulocytopenia). Leukostasis affecting brain and lung may also occur. Death occurs commonly due to severe pancytopenia and resulting infections. Refractory (resistant) disease is defined as those patients who fail to obtain a complete response with induction therapy, ie, failure to eradicate all detectable leukemia cells (<5% blasts) from the bone marrow and blood with subsequent restoration of normal hematopoiesis (>25% marrow cellularity and normal peripheral blood counts). Relapsed disease describes the reappearance of leukemia cells in the bone marrow or peripheral blood after the attainment of a complete remission.

Minimal residual disease (MRD) refers to the presence of disease in cases deemed to be in complete remission by conventional pathologic analysis. MRD positivity is defined as the presence of 0.01% or more ALL cells and has been shown to be a strongest prognostic factor to predict the risk of relapse and death when measured during and after induction therapy in both newly diagnosed and relapsed ALL. In a meta-analysis of 20 studies of 11,249 pediatric ALL, Berry et al (2017) reported a hazard ratio for event-free survival in MRD-negative patients compared with MRD-positive patients of 0.23 (95% confidence interval, 0.18 to 0.28).\(^1\)
Approximately 5000 cases of B-cell ALL are diagnosed every year in the United States, and approximately 620 pediatric and young adult patients with B-cell ALL will relapse each year in the United States. B-cell ALL is largely a disease of the young, with approximately 60% of cases occurring in patients younger than 20 years old with a median age at diagnosis of 15 years.

**Treatment**

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

**DIFFUSE LARGE B-CELL LYMPHOMA**

Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin lymphoma and accounts for approximately 25% of non-Hodgkin lymphoma cases. DLBCL exhibits large heterogeneity in morphologic, genetic, and clinical aspects and multiple clinicopathologic entities are defined by the 2016 World Health Organization classification, which are sufficiently distinct to be considered separate diagnostic categories. Teras et al (2016) has estimated that 27,650 new cases of DLBCL were diagnosed in the United States in 2016.

**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%. However, based on a number of prognostic factors, 20% to 50% of DLBCL cases are refractory or relapse after first-line chemotherapy. 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. 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. Nonspecific, polyclonal proliferation of lymphocytes by cytokines (immune system growth factors), also called autolymphocyte therapy, increases the number of activated lymphocytes.

**T Lymphocytes and Killer Cells**

Initially, this treatment was performed by harvesting peripheral lymphokine-activated killer cells and activating them in vitro with the T-cell growth factor interleukin-2 and other cytokines. More recent techniques have yielded select populations of cytotoxic T lymphocytes with specific reactivity to tumor
Peripheral lymphocytes are propagated in vitro with antigen-presenting dendritic cells that have been pulsed with tumor antigens. Alternatively, innate tumor-infiltrating lymphocytes (TIL) from the tumor biopsy are propagated in vitro with interleukin-2 and anti-CD3 antibody, a T-cell activator. Expansion of TIL for clinical use is labor intensive and requires laboratory expertise. Only a few cancers are infiltrated by T cells in significant numbers; of these, TIL can be expanded in only approximately 50% of cases. These factors limit the widespread applicability of TIL treatment. Recently, cytokine-induced killer cells have been recognized as a new type of antitumor effector cells, which can proliferate rapidly in vitro, with stronger antitumor activity and a broader spectrum of targeted tumors than other reported antitumor effector cells.\textsuperscript{15}

**Cellular Therapy and Dendritic Cell Infusions**

The major research challenge in adoptive immunotherapy is to develop immune cells with antitumor reactivity in quantities sufficient for transfer to tumor-bearing patients. In current trials, 2 methods are studied: adoptive cellular therapy and antigen-loaded dendritic cell infusions.

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

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

Dendritic cell-based immunotherapy uses autologous dendritic cells (ADC) to activate a lymphocyte-mediated cytotoxic response against specific antigens in vivo. ADCs harvested from the patient are either pulsed with antigen or transfected with a viral vector bearing a common cancer antigen. The activated ADCs are then retransfused into the patient, where they present antigen to effector lymphocytes (CD4-positive T-cells, CD8-positive T-cells, and in some cases, B cells). This initiates a cytotoxic response against the antigen and against any cell expressing the antigen. In cancer immunotherapy, ADCs are pulsed with tumor antigens; effector lymphocytes then mount a cytotoxic response against tumor cells expressing these antigens. (See evidence review 8.01.53 for a discussion of dendritic cell-based immunotherapy for prostate cancer.)

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

Note: Allogeneic cell transplantation following nonmyeloablative conditioning of the recipient (known as reduced-intensity conditioning) also may be referred to as “adoptive immunotherapy” in the literature. However, reduced-intensity conditioning cell transplantation relies on a donor-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 cell transplantation.

**Tisagenlecleucel**

Tisagenlecleucel is an adoptive immunotherapy in which the T cells of a patient are modified by genetic engineering using a lentiviral vector. The resulting genetic modified cells express a CD-19-directed chimeric antigen receptor protein that consists of an extracellular portion that has a murine anti-CD19
single-chain antibody fragment as well as an intracellular portion that contains T-cell signaling and co-stimulatory domains. Once injected, the genetically modified T cells selectively target and bind to CD19 antigen expressed on the surface of B cells and tumors derived from B cells. Subsequently, the intracellular signaling domains play crucial roles in T-cell activation, persistence, and effector functions.17

Axicabtagene Ciloleucel
Similar to tisagenlecleucel, axicabtagene ciloleucel is an adoptive immunotherapy in which the T cells of a patient are modified genetically using a retroviral vector. The resulting genetically modified cells express a CD-19-directed chimeric antigen receptor protein that has a murine single-chain variable fragment with specificity for CD19. Once injected, the genetically modified T cells selectively target and bind to CD19 antigen expressed on the surface of normal and malignant B cells.18

REGULATORY STATUS
On August 30, 2017, tisagenlecleucel (Kymriah™; Novartis) was approved by 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 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 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 December 1996 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through June 14, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to 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 a technology, 2 domains are examined: the relevance and the 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.

Adoptive immunotherapy has been investigated for the treatment of relatively common cancers in which novel treatments have been adopted when RCTs show efficacy. Selected studies include only new RCTs.
ADOPTIVE IMMUNOTHERAPY MODALITIES

Three systematic reviews on adoptive immunotherapy combining studies using different adoptive immunotherapy methods have been published. Conditions treated in these reviews were renal cell carcinoma\(^1\) and postoperative hepatocellular carcinoma.\(^2\)\(^3\)

CYTOTOXIC T LYMPHOCYTES

Epstein-Barr Virus–Associated Cancers

Bollard et al (2014) conducted an international prospective cohort study of cytotoxic T lymphocyte (CTL) therapy in patients with Epstein-Barr virus (EBV)–positive Hodgkin or non-Hodgkin lymphoma.\(^2\) Patients had either active, relapsed disease (n=21) or were in remission with a high risk of relapse (n=29). CTLs with activity against EBV antigens were generated by incubating peripheral blood monocytes with EBV antigen-infected dendritic cells (DCs). Eleven (52%) of 21 patients with active disease achieved complete response (CR), and 2 (10%) patients achieved partial response; 2-year event-free survival in this cohort was approximately 50%. Twenty-seven (93%) of 29 patients in remission achieved CR; 2-year event-free survival was 82%. Immediate or delayed toxicity related to CTL infusion was not observed.

Chia et al (2014) studied 35 patients with EBV-positive nasopharyngeal cancer at a single center in China.\(^2\) Patients received standard chemotherapy with gemcitabine and carboplatin followed by EBV-specific CTL infusion. Median progression-free survival (PFS) and overall survival (OS) were 8 months and 30 months, respectively. One-, 2-, and 3-year OS rates were 77%, 63%, and 37%, respectively. In comparison, median OS in a group of similar historical controls treated at the same institution with chemotherapy only was 18 to 21 months, and 2- and 3-year OS rates were 30% to 43% and 16% to 25%, respectively. The most common adverse events associated with CTL infusion were grade 1 and 2 fatigue and grade 1 myalgia. Two patients developed transient fever, and 3 patients developed grade 1 skin rash. Grade 3 or higher hematologic or nonhematologic toxicities were not observed during CTL therapy. In a Japanese series of 7 patients who received CTLs for advanced oral and maxillofacial cancers, Ohtani et al (2014) reported 1-year survival rates in patients who achieved response (n=3) and in those with progressive disease (n=4) of 100% and 25%, respectively, although definitions of response were unclear.\(^2\)

Subsection Summary: Epstein-Barr Virus–Associated Cancers

Two small, prospective noncomparative cohort studies in patients with relapsed disease have indicated a response to infused CTLs directed against cancer-associated viral antigens. Adverse events were mild or moderate. There are no RCTs comparing CTL with the standard of care and therefore no conclusions can be made about the efficacy of CTL in EBV-associated cancers. To establish efficacy, the following are needed: large, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit.

Cytomegalovirus-Associated Cancers

Schuessler et al (2014) administered CTLs with or without chemotherapy to 13 patients with recurrent glioblastoma multiforme.\(^2\) CTLs with activity against Cytomegalovirus were generated by incubating peripheral blood monocytes with synthetic peptide epitopes. Median OS was 1.1 years (range, 4.4 months to 6.6 years). Adverse events were minor.

Subsection Summary: Cytomegalovirus-Associated Cancers

A single case series in 13 patients with glioblastoma multiforme treated with CTL has reported mild adverse events. There are no RCTs comparing CTL with the standard of care and therefore no
conclusions can be made about the efficacy of CTL in *Cytomegalovirus*-associated cancers. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit.

**CYTOKINE-INDUCED KILLER CELLS**

**Nasopharyngeal Carcinoma**

Li et al (2012) conducted an RCT to evaluate the efficacy of autologous cytokine-induced killer (CIK) transfusion in combination with gemcitabine and cisplatin (GC) chemotherapy to treat nasopharyngeal carcinoma in patients with distant metastasis after radiotherapy. From 2007 to 2008, 60 patients with distant metastasis after radiotherapy were followed in a university cancer center in China. Patients were randomized to 2 groups; 30 patients in the GC plus CIK group received adoptive autologous CIK cell transfusion in combination with GC chemotherapy, and 30 patients in the GC group received chemotherapy alone. One- and 2-year OS rates were 90% (27/30) and 70% (21/30), respectively, in the GC plus CIK group vs 83% (25/30) and 50% (15/30), respectively, in the GC group. Mean OS was 31 months for the GC plus CIK group and 26 months for the GC group (p=0.137). Median PFS was 26 months for the GC plus CIK group and 19 months for the GC group (p=0.023). This small, single-center RCT suggests that the combination of CIK cells and GC regimen chemotherapy may be a viable treatment option for patients with advanced nasopharyngeal carcinoma.

**Subsection Summary: Nasopharyngeal Carcinoma**

A single RCT from China reported numerically favorable but statistically insignificant effect on PFS and OS. This body of evidence is limited by the context of the studies (non-U.S.), small sample size, and other methodologic weaknesses (inadequate reporting of randomization, allocation concealment, and power). To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit.

**Renal Cell Carcinoma**

Liu et al (2012) conducted an RCT to evaluate the effects of autologous CIK cell immunotherapy in patients with metastatic renal cell carcinoma followed in another university cancer center in China. From 2005 to 2008, 148 patients were randomized to autologous CIK cell immunotherapy (arm 1, n=74) or interleukin-2 (IL-2) treatment combination with human interferon-α-2a (arm 2, n=74). The primary end point was OS, and the secondary end point was PFS evaluated by Kaplan-Meier analyses and hazard ratios (HRs) with Cox proportional hazards models. Three-year PFS and OS rates in arm 1 were 18% and 61%, respectively, vs 12% and 23%, respectively, in arm 2 (p=0.031 and p<0.001, respectively). Median PFS and OS in arm 1 were significantly longer than those in arm 2 (PFS, 12 months vs 8 months, p=0.024; OS, 46 months vs 19 months, p<0.001, respectively). Multivariate analyses indicated that the cycle count of CIK cell immunotherapy as a continuous variable was significantly associated with prolonged PFS (HR=0.88; 95% confidence interval [CI], 0.84 to 0.93; p<0.001) and OS (HR=0.58; 95% CI, 0.48 to 0.69; p<0.001) in arm 1. These findings suggest that CIK cell immunotherapy has the potential to improve the prognosis of patients with metastatic renal cell carcinoma.

Zhang et al (2013) conducted a small RCT in China that assessed 20 patients who had unilateral, locally advanced renal cell carcinoma after nephrectomy. Patients were randomized 1:1 to postoperative CIK therapy or usual care (chemotherapy with or without radiotherapy, additional surgery, or no further treatment). Method of randomization was not described. At a median follow-up of 44 months, 6 patients in the CIK group and 5 controls achieved CR; 2 patients in the CIK group and no controls
achieved partial response (overall objective response, 80% in the CIK group and vs 50% the control group; \(p=0.175\)). Mean PFS was significantly longer in the CIK group, but OS was not (mean PFS, 32 months vs 22 months; \(p=0.032\); mean OS, 35 months vs 34 months; \(p=0.214\)). Adverse events included mild arthralgia, laryngeal edema, fatigue, and low-grade fever in 3 patients. Grade 3 or higher adverse events were not observed.

Zhao et al (2015) conducted an RCT in China among operable and inoperable patients with renal cell carcinoma.\(^9\) Dendritic cells were also incorporated into treatment. Among the 60 operable patients, the 3-year disease-free survival (DFS) rate was 96.7% compared with 57.7% in the control group. PFS was also longer in the CIK group (\(p=0.021\)). Among the 62 inoperable patients, OS was longer in the CIK group (\(p=0.012\)). No severe adverse reactions were observed.

**Subsection Summary: Renal Cell Carcinoma**

Three RCTs from China have evaluated the efficacy of CIK cell immunotherapy in renal cell carcinoma. The largest of the 3 RCTs reported statistically significant gains in PFS and OS with CIK cell immunotherapy compared with IL-2 plus interferon-\(\alpha\)-2. This body of evidence is limited by the context of the studies (non-U.S.) and choice of a nonstandard comparator. The other 2 RCTs also reported response rates in favor of CIK therapy with inconsistent effects on survival. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit.

**Gastric Cancer**

Shi et al (2012) in China published a nonrandomized, comparative study to determine the long-term efficacy of adjuvant immunotherapy with autologous CIK cells in 151 patients with locally advanced gastric cancer.\(^30\) Five-year OS and 5-year DFS rates for immunotherapy vs no immunotherapy (control group) were 32% vs 23% (\(p=0.07\)) and 28% vs 10% (\(p=0.04\)), respectively. For patients with intestinal-type tumors, 5-year OS (47% vs 31%; \(p=0.045\)) and DFS (42% vs 16%; \(p=0.02\)) rates were significantly higher for immunotherapy.

**Subsection Summary: Gastric Cancer**

A single nonrandomized prospective study from China has reported statistically significant effects on DFS and OS in favor of immunotherapy with autologous CIK vs no immunotherapy. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit.

**Colorectal Cancer**

Zhao et al (2016) reported the results of a controlled trial in which 122 patients with metastatic colorectal cancer were randomized to CIK cell immunotherapy plus chemotherapy \((n=61)\) or chemotherapy alone \((n=61)\).\(^31\) The primary study end point was OS. The median OS was significantly greater with CIK cell immunotherapy plus chemotherapy (36 months) than with chemotherapy alone (16 months; \(p<0.001\)). The 3-year OS rates for both groups were 48% and 23%, respectively (\(p<0.001\)).

**Subsection Summary: Colorectal Cancer**

A single RCT from China has reported a statistically significant effect on OS in favor of immunotherapy with CIK immunotherapy vs chemotherapy alone. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments,
centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit.

**Hepatocellular Carcinoma**

Cai et al (2017) reported the results of a meta-analysis of 9 RCTs and 3 quasi-RCTs that compared outcomes of conventional treatments plus sequential CIKs with conventional treatments alone (total N=1387 patients). None of the 12 studies were rated as low risk of bias in all 7 domains as assessed by the Cochrane risk of bias tool. Of the 12 RCTs and quasi-RCTs, 5 reported a statistically significant favorable survival benefit for patients receiving conventional treatments plus sequential CIKs. All 12 studies were from Asia (1 Japan, 1 Korea, 10 China). Results of a meta-analysis reported a statistically significant reduction in the hazard of death by 41% (HR=0.59; 95% CI, 0.46 to 0.77; p<0.005). However, the heterogeneity among the included studies was statistically significant (p=0.03, I²=48).

Yu et al (2014) conducted an RCT in China of 132 patients who had previously untreated HCC. Patients were randomized 1:1 to CIK therapy plus standard treatment (surgical resection in eligible patients, local treatment, or best supportive care) or standard treatment only. At a median follow-up of 19 months, median PFS was 14 months in the CIK group and 7 months in the control group (p=0.019). Estimated 1-, 2-, and 3-year PFS rates were 56% vs 35% (p=0.004), 36% vs 18% (p=0.004), and 27% vs 18% (p=0.017), respectively, favoring CIK therapy. Median OS was 25 months in the CIK group vs 11 months in the control group (p=0.008). Estimated 1-, 2-, and 3-year OS rates were significantly higher for immunotherapy: 74% vs 50% (p=0.002), 53% vs 30% (p=0.002), and 42% vs 24% (p=0.005), respectively. In the subgroup of operable patients, 3-year and median OS did not differ statistically between groups. Common adverse events attributed to CIK therapy were grade 1 or 2 fever, allergy, and headache. Grade 3 or 4 adverse events were not observed. A nonrandomized study from China by Cui et al (2014) reported improved PFS in 30 patients who received radiofrequency ablation plus CIK/natural killer cell/gamma delta T-cell (a type of tumor-infiltrating lymphocytes [TIL]) infusion (median PFS, not reached) compared with 32 patients who received radiofrequency ablation alone (median PFS, 12.0 months).

Lee et al (2015) conducted an RCT in Korea of 230 patients being treated for HCC by surgical resection, radiofrequency ablation, or percutaneous ethanol injection. Patients were randomized 1:1 to adjuvant CIK cell injections 16 times during 60 weeks or to no adjuvant therapy. The primary end point was recurrence-free survival; secondary end points included OS and cancer-specific survival. The median recurrence-free survival was 44 months in the CIK group and 30 months in the control group (p=0.010). OS was longer in the CIK group than in the control group (HR=0.21, p=0.008). Cancer-specific survival was longer in the CIK group than in the control group (HR=0.19, p=0.02). Adverse events occurred more frequently in the CIK group than in the control group, but grade 3 or 4 adverse events did not differ significantly between groups. Adverse events associated with CIK included pyrexia, chills, myalgia, and fatigue.

**Subsection Summary: Hepatocellular Carcinoma**

Several RCTs and quasi-RCTs have evaluated the efficacy of CIK cells in HCC. These studies have generally reported some benefits in response rates and/or survival. Results of a meta-analysis of these trials also reported a statistically significant reduction in the hazard of death by 41%, but there was considerable heterogeneity among the included studies. Most trials were from Asia and did not use the standard of care as the control arm. This body of evidence is limited by the context of the studies (non-U.S.), small sample sizes, heterogeneous treatment groups, and other methodologic weaknesses. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate
randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit.

Non-Small-Cell Lung Cancer
Wang et al (2014) conducted a systematic review of RCTs of CIK cells for the treatment of non-small-cell lung cancer (NSCLC). Overall, 17 RCTs (total N=1172 patients) were included in the analysis. The studies generally had small sample sizes; the largest had 61 CIK-treated patients and 61 control patients. Most studies also incorporated DC therapy. All were conducted in China. A significant effect of CIK was found for the median time to progression and median survival time. OS at various time points significantly favored CIK.

Subsection Summary: Non-Small-Cell Lung Cancer
A single systematic review of RCTs of CIK cells for the treatment of NSCLC that included trials conducted in China reported some benefits in median time to progression and median survival time. The included body of evidence trials in the systematic review is limited by the context of the studies (non-U.S.), small sample sizes, heterogeneous treatment groups, and other methodologic weaknesses. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit.

TUMOR-INFILTRATING LYMPHOCYTES
Dudley et al (2008) conducted a series of nonrandomized phase 2 studies examining TIL plus IL-2 in patients with metastatic melanoma under various conditions of preinfusion lymphodepletion. A nonmyeloablative 7-day chemotherapy regimen (n=43) was compared with ablative regimens comprising 5-day chemotherapy plus either 200 centigray (cGy; n=25) or 1200 cGy (n=25) total-body irradiation. Ninety-five percent of patients had progressive disease after prior systemic treatment. Objective response rates (ORRs) by Response Evaluation Criteria in Solid Tumors were 49%, 52%, and 72%, respectively, and did not differ significantly among groups. Responses occurred at multiple metastatic sites, including the brain, and many were durable; 10 patients who achieved CR had no relapse at a median follow-up of 31 months. Toxicities of treatment occurred primarily in the 1200-cGy group and included a delay in marrow recovery of 1 to 2 days compared with the other treatment groups, somnolence requiring intubation, renal insufficiency, and posterior uveitis. Rosenberg et al (2011) reported updated results of these patients with median follow-up of 62 months. Ten patients who previously had been classified as partial responders were reclassified as complete responders by Response Evaluation Criteria in Solid Tumors (1, 3, and 6 patients in the nonmyeloablative, 200-cGy, and 1200-cGy groups, respectively). Of these 20 patients (22% of the original cohort), 19 (95%) had ongoing complete regression longer than 3 years. Actuarial 3- and 5-year survival rates for the entire group were 36% and 29%, respectively, but for the 20 complete responders, 100% and 93%, respectively. Likelihood of achieving a CR was similar regardless of prior therapy.

Dreno et al (2002) conducted an RCT of 88 patients with malignant melanoma without detectable metastases who were randomized to TIL plus IL-2 or to IL-2 alone. There was no significant difference in the duration of relapse-free interval or OS. Figlin et al (1999) randomized 178 patients with metastatic renal cell carcinoma or resectable renal tumors to adjuvant continuous low-dose IL-2 therapy, with or without additional TIL. TILs were harvested from surgical specimens. Outcomes were similar in both groups and, for this reason, the trial was terminated early.
**Section Summary: Tumor-Infiltrating Lymphocytes**

One small RCT compared TILs plus IL-2 with IL-2 alone in patients with nonmetastatic melanoma and reported no difference between treatment groups in relapse or survival outcomes. Cohort studies in patients with refractory metastatic melanoma demonstrated response rates of 49% and 52% to 72% with TIL plus nonmyeloablative or myeloablative regimens, respectively. Durable responses in most of the patients who achieved CR were observed beyond 3 years. Toxicities appeared primarily associated with the myeloablative regimen. Larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and use of an appropriate standard of care as control arm showing treatment benefit are needed to establish.

**DENDRITIC CELLS**

Antigen-loaded autologous dendritic cells (ADCs) have been explored primarily in early-stage trials in various malignancies including lymphoma,\(^41\) myeloma,\(^42,43\) subcutaneous tumors,\(^44\) melanoma,\(^45\) NSCLC,\(^46,47\) renal cell cancer,\(^48\) and cervical cancer.\(^49\) A systematic review by Tanyi and Chu (2012) highlighted progress in DC-based immunotherapy in epithelial ovarian cancer.\(^50\)

**Glioblastoma Multiforme**

Bregy et al (2013) published a systematic review of observational studies of active immunotherapy using ADCs in the treatment of glioblastoma multiforme.\(^51\) Twenty-one studies published through early 2013 were included in this review (total N=403 patients). Vaccination with DCs loaded with autologous tumor cells resulted in an increased median OS in patients with recurrent disease (72-138 weeks across 8 studies), as well as in those newly diagnosed (65-230 weeks across 11 studies) compared with average survival of 58 weeks. Complications and safety of the vaccine were assessed in all studies. No study indicated any sign of autoimmune reaction. Most adverse events were injection-site reactions (22%). Other adverse events included fatigue (19.5%), constipation/diarrhea (1.6%), myalgia/malaise (1.6%), shivering (1.4%), and vomiting (0.5%).

Liu et al (2018) reported on interim results of an RCT of 331 newly diagnosed glioblastoma patients initially treated with surgery and chemoradiotherapy who were randomized to temozolomide plus ADC vaccine or temozolomide plus placebo.\(^52\) The interim results reported on a blinded analysis of all patients because sufficient events of disease progression and/or death had not occurred yet. More than 90% of patients in the placebo arm received experimental treatment after documented progression. The blinded median OS of both treatment arms combined (23.1 months) in the RCT was compared with historical controls (15-17 months). These results are premature.

**Subsection Summary: Glioblastoma Multiforme**

A systematic review of observational studies has examined the role of ADC-based adoptive immunotherapy in glioblastoma multiforme. Because of the observational and noncomparative nature of the available evidence, the review was subject to publication and selection bias, which has the potential to lessen or amplify the true effect of adoptive immunotherapy. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. Interim results from one such RCT have been published and are uninformative because patients were unblinded and results combined for treatment and placebo arms.

**Non-Small-Cell Lung Cancer**

Shi et al (2012) conducted an RCT at a university cancer center in China to evaluate the role of combination DC plus CIK immunotherapy as a maintenance treatment of advanced NSCLC.\(^46\) From 2008...
to 2010, 60 patients with stage IIIb or IV disease after treatment with 4 cycles of a platinum-based chemotherapy regimen were randomized into 2 groups. One group was treated with DC plus CIK cell therapy (n=30), and the control group no adoptive immunotherapy (n=30). Outcome measures were PFS and adverse events of treatment. PFS was 3.2 months in the DC plus CIK group (95% CI, 2.9 to 3.5 months) vs 2.6 months control group (95% CI, 2.39 to 2.73 months; p<0.05). No significant toxic reactions were observed in the DC plus CIK group, including bone marrow toxicity and gastrointestinal reactions. The findings of this small single-center RCT would indicate that combination immunotherapy with dendritic and CIK cells may offer a viable option as maintenance therapy for patients with advanced NSCLC.

Chen et al (2014) in China conducted a systematic review and meta-analysis of RCTs that compared combination DC plus CIK immunotherapy with any other treatment (placebo, no intervention, conventional treatment, or other complementary and alternative medicines) for any cancer type and stage. Two RCTs compared DC plus CIK and chemotherapy with chemotherapy alone in patients with stage III or IV NSCLC and reported OS estimates (total N=150). Pooled relative risk favored DC plus CIK therapy at 2 years but not at 1 year (relative risk for 1-year OS=1.38; 95% CI, 1.00 to 1.90; p=0.05; I²=35%; relative risk for 2-year OS=2.88; 95% CI, 1.38 to 5.99; p=0.005; I²=0%).

The 2014 systematic review by Wang (discussed previously) also included many studies that used DC in combination with CIK.

**Subsection Summary: Non-Small-Cell Lung Cancer**
Two RCTs and a meta-analysis of these RCTs have evaluated the efficacy of DC plus CIK cells in NSCLC. The RCTs generally reported some benefits in response rates and/or survival. Results of a meta-analysis of these trials also reported a statistically significant reduction in the hazard of death. However, the effect was inconsistent. Most were from Asia and did not use the standard of care as the control arm. This body of evidence is limited by the context of the studies (non-U.S.), small sample sizes, heterogeneous treatment groups, and other methodologic weaknesses. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit.

**Medullary Thyroid Cancer**
In a phase 1 pilot study, Bachleitner-Hofman et al (2009) reported on 10 patients with metastatic medullary thyroid cancer (MTC) treated with ADCs pulsed with allogeneic MTC tumor cell lysate. At a median follow-up of 11 months, 3 (30%) patients had stable disease, and 7 (70%) patients progressed. No World Health Organization grade 3 or 4 toxicities or autoimmune reactions were observed. Of note, human leukocyte antigen match between patients and tumor cell lines did not predict disease stabilization or progression, suggesting that, should future studies demonstrate the efficacy of ADC therapy for MTC using allogeneic tumor lysate, an unlimited source of tumor material may be available for lysate preparation.

**Subsection Summary: Medullary Thyroid Cancer**
A small prospective noncomparative study in 10 MTC patients treated with ADCs has been published. There are no RCTs comparing DC-based adoptive immunotherapy with the standard of care and therefore no conclusions can be made. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit.
Pancreatic Cancer

In a phase 1 study, Hirooka et al (2009) assessed 5 patients with inoperable pancreatic cancer reinfused ADCs and lymphokine-activated killer cells with gemcitabine; antigen priming of the ADCs was presumed to occur in vivo from apoptosis of gemcitabine-exposed tumor cells. One patient had a partial response, two had stable disease for more than 6 months, and two had disease progression. Toxicities included grade 1 anemia and grade 2 leukocytopenia, nausea, and constipation.

Subsection Summary: Pancreatic Cancer

A small prospective noncomparative study in 5 patients with pancreatic cancer treated with ADCs and lymphokine-activated killer has been published. There are no RCTs comparing DC-based adoptive immunotherapy with the standard of care and therefore no conclusions can be made. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight and the use of an appropriate standard of care as the control arm showing treatment benefit.

Genetically Engineered T Cells

Engineered T cell–based antitumor immunotherapy uses gene transfer of tumor antigen-specific T-cell receptors (TCR) or synthetic chimeric antigen receptors. Review articles have highlighted recent progress in this field for solid and hematologic malignancies.

TCR Therapy

In a phase 2 study, Johnson et al (2009) transfected autologous peripheral lymphocytes of 36 patients who had metastatic melanoma with genes encoding TCRs highly reactive to melanoma/melanocyte antigens (MART-1:27-35 and gp100:154-162). Nine (25%) patients experienced an objective response; 8 patients had a partial response lasting 3 months to more than 17 months, and 1 patient (in the gp100 group) had a CR lasting more than 14 months. Treatment toxicities included erythematous rash, anterior uveitis, hearing loss, and dizziness, suggesting that these were attributable to recognition by the genetically modified lymphocytes of normally quiescent cells expressing the targeted cancer antigens; melanocytic cells exist in the skin, eye, and the inner ear. Ideal targets for TCR gene therapy may be antigens that arise in cancers of nonessential organs (eg, prostate, ovary, breast, thyroid) or are not expressed on normal adult tissues (eg, cancer-testes antigens).

Additional studies have examined TCR gene therapy in Hodgkin and non-Hodgkin lymphoma, prostate tumors, and neuroblastoma.

Subsection Summary: TCR Therapy

One small cohort study in patients with metastatic melanoma reported a 25% response rate with TCR gene therapy and broad treatment-related toxicities. This evidence does not demonstrate net health benefit with genetically engineered T cells in patients with metastatic melanoma.

Tisagenlecleucel

B-Cell Acute Lymphoblastic Leukemia

Pivotal Trials

In the pivotal trial phase 2 single-arm, international, multicenter trial (study B2202), 68 patients ages 3 to 21 years at screening, with CD19-positive second or greater bone marrow relapse or primary refractory B-cell acute lymphoblastic leukemia were treated with tisagenlecleucel and followed for 12 months. Trial results have not been published; data were obtained from the Food and Drug
Administration (FDA) Oncologic Drugs Advisory Committee Meeting held in July 2017. Sixty-three patients received U.S.-manufactured product while 5 patients received EU-manufactured product. Patients were required to have more than 5% blasts at screening and either ineligible for or have relapsed after allogeneic cell transplant. Refractory was defined by not achieving an initial CR after 2 cycles of a standard chemotherapy regimen (primary refractory). Subjects who were refractory to subsequent chemotherapy regimens after an initial remission were considered chemo-refractory.

The prespecified primary efficacy end point 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 3 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 best objective remission rate (CR or CRI with minimal residual disease [MRD]–negative bone marrow) within 3 months of receiving tisagenlecleucel. Key secondary end points were tested sequentially (after primary end point was significant) to control for overall type I error.

Of the 107 patients who were screened, 88 met the trial inclusion criteria and of these 68 (77.3%) were infused with tisagenlecleucel. In 7 (8%) patients, tisagenlecleucel could not be manufactured. The median time from enrollment to infusion was 44 days. Of the 68 patients, 63 patients received tisagenlecleucel infusion at least 3 months prior to the data cutoff date. 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. The median age was 12 years (range, 3-23 years), 82% were male, 75% were white, median Karnofsky/Lansky Performance Status score was 90 (range, 50-100), 79% had relapsed disease, 12% had chemo-refractory disease, and 9% had primary refractory disease. The enrolled patient population was heavily pretreated as evident by the following statistics; 87% (59) of patients had received a prior hematopoietic cell transplant with a median of 3 previous treatments. Results summarized in Table 1 show that 52 (82.5%) patients who received tisagenlecleucel infusion achieved a CR or CRI within 3 months. Of the 52 patients who achieved a CR or CRI within 3 months, 29 (56%) were still in remission, 13 (25%) had relapsed, 12 (23%) were censored prior to the data cutoff. The reasons for censoring were 6 received hematopoietic cell transplant, 5 received a new cancer therapy, and 1 was lost to follow-up. The estimated relapse-free rate among responders at month 6 was 75.4% (95% CI, 57.2% to 86.7%). Among the responders, 4 died (3 after disease relapse, 1 after new cancer therapy was initiated while in remission).

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Results, n (%) (95% Confidence Interval) or %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary end point (3 mo)</strong></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>63</td>
</tr>
<tr>
<td>Objective remission rate (CR + CRI)</td>
<td>52 (82.5) (70.9 to 91.0)</td>
</tr>
<tr>
<td>CR</td>
<td>40 (63)</td>
</tr>
<tr>
<td>CRI</td>
<td>12 (19)</td>
</tr>
<tr>
<td>Not reported/unknown</td>
<td>11 (17.5)</td>
</tr>
<tr>
<td><strong>Secondary end point (3 mo)</strong></td>
<td></td>
</tr>
<tr>
<td>Best objective remission rate (Cr + CRI with MRD-positive)</td>
<td>52 (82.5) (70.9 to 91.0)</td>
</tr>
<tr>
<td><strong>Other secondary end points</strong></td>
<td></td>
</tr>
<tr>
<td>Median duration of remission</td>
<td>Not reached</td>
</tr>
<tr>
<td>Median event-free survival</td>
<td>Not reached</td>
</tr>
</tbody>
</table>

Original Policy Date: December 1996
Outcomes | Results, n (%) (95% Confidence Interval) or %
--- | ---
Percent relapse-free at 6 mo after remission | 75
Percent survival at 6 mo | 89
Percent survival at 9 mo | 79
Percent survival at 12 mo | 79

Adapted from Food and Drug Administration (n.d.) and (2017).\textsuperscript{64,65}
CR: complete remission; CRI: complete remission with incomplete blood count recovery; MRD: minimal residual disease.

**Supportive Studies**
Two single-arm studies (total N=84 patients) were conducted using a product manufactured at a university cell and vaccine production facility.\textsuperscript{66,67} The first study was a phase 1/2a single-center study in 55 patients enrolled between 2012 and 2015. The ORR rate (CR or CRI) was 95% (52/55), and best ORR (CR or CRI with MRD-negative bone marrow) was 89% (49/55). Median OS was 32.7 months (95% CI, 21.0 months to inestimable). The first pediatric patient treated in the study has been in remission for 5 years. The second study was a phase 2 multicentric study that enrolled 29 patients between 2014 and 2016. The ORR rate (CR or CRI) was 69% (20/29).

**Safety**
Safety data included 68 patients (63 patients received who U.S.-manufactured product plus 5 patients who received EU-manufactured product) and is summarized in Tables 2 and 3.\textsuperscript{64,65} Cytokine release syndrome (CRS) was the most common serious life-threatening adverse event in the pivotal study and required aggressive supportive measures. One fatality due to CRS-related coagulopathy was observed in the pivotal study. Any grade CRS occurred in 78% (53/68) patients while 47% (32/68) experienced a grade 3 or 4 CRS. The severity of CRS was associated with high tumor burden of greater than 50% blasts in the bone marrow at screening. CRS occurred after a median of 3 days (range, 1-22 days) after tisagenlecleucel infusion and lasted for a median duration of 8 days. CRS resulted in significant morbidity burden as indicated by intensive care unit admission (31 [46%]), ventilatory support (10 [15%]), dialysis (7 [10%]), hypotension (35 [51%]), and hypotension requiring high-dose vasopressor support (17 [25%]).

The next most important adverse event of tisagenlecleucel was neurotoxicity such as encephalopathy and seizures. Any grade neurotoxicity was reported in 44% (30/68) patients, and grade 3 neurotoxicity was reported in 15% (10/68) patients. No cases of grade 4 neurotoxicity were reported. Although neurotoxicity was reversible with the use of optimal and best supportive care, the severity of these toxicities requires monitoring for airway protection.

FDA also noted infection as a special adverse event of interest. In the first 8 weeks after infusion, 43% (29/68) of patients developed an infection of which 24% (16/68) were grade 3 and 3% (2/68) were grade 4. Infection included gram-positive, gram-negative systemic infections, Clostridium difficile, candida, herpes simplex, and encephalitis due to herpesvirus 6. Three deaths occurring within 60 days and related to infection with herpesvirus 6, bacterial infection, and fungal sepsis was reported.

Other adverse events of special interest included prolonged cytopenia, cardiac disorders, and B-cell aplasia. Three patients experienced congestive heart failure that required treatment. Most patients in the pivotal trial had previously been treated with chemotherapy and radiotherapy that predisposed them to cardiotoxicity; it is an anticipated risk in the intended population that would receive treatment with tisagenlecleucel. Acquired hypogammaglobulinemia is an expected side effect of tisagenlecleucel because it not only kills pre-B acute lymphoblastic leukemia cells but also normal B cells because they are CD19-positive. Patients in the trial were maintained on supplemental treatment with intravenous
gamma globulin after tisagenlecleucel. It is unclear as to how long intravenous gamma globulin would be required.

Multiple design features of the tisagenlecleucel retroviral vector such as minimal homology between packaging plasmids and vector sequences, segregation on 4 different DNA plasmids, deletion of HIV accessory genes, and use of “self-inactivating” vector design aim to reduce the risk the potential of replication-competent virus generation and insertional mutagenesis. However, the theoretical risk of formation of replication-competent virus, their clonal growth or neoplastic transformation of transduced cells cannot be ruled out. If approved, each vector batch and production cells will be tested for the presence of replication-competent retrovirus. However, Novartis does not plan to collect patient samples for replication competent retrovirus testing. It is expected that, over next 5 years, approximately 5000 patients may be enrolled in the first 5 years in a postmarketing registry that will follow-up patients up to 15 years after tisagenlecleucel infusion.

Table 2. Summary of Serious Adverse Events (>5% Patients) in the Pivotal Study

<table>
<thead>
<tr>
<th>Serious Adverse Event</th>
<th>Results, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>68</td>
</tr>
<tr>
<td>Cytokine release syndrome</td>
<td>43 (63)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>14 (21)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>8 (12)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Fever</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>4 (6)</td>
</tr>
</tbody>
</table>

Adapted from Food and Drug Administration (n.d.; 2017). 64,65

a Any adverse event that resulted in death or was life-threatening or required inpatient hospitalization or caused prolongation of existing hospitalization or resulted in persistent or significant disability/incapacity or was a congenital anomaly/birth defect, or required intervention to prevent permanent impairment or damage.

Table 3. Summary of Adverse Events of Special Interest in 68 Patients in the Pivotal Study

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Grade 3, n (%)</th>
<th>Grade 4, n (%)</th>
<th>All Grades, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least 1 event</td>
<td>23 (34)</td>
<td>14 (21)</td>
<td>37 (54)</td>
</tr>
<tr>
<td>Cytokine release syndrome</td>
<td>16 (24)</td>
<td>10 (15)</td>
<td>26 (39)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>12 (18)</td>
<td>3 (4)</td>
<td>15 (22)</td>
</tr>
<tr>
<td>Hematopoietic cytopenia not resolved by day 28</td>
<td>2 (3)</td>
<td>10 (15)</td>
<td>12 (18)</td>
</tr>
<tr>
<td>Infections</td>
<td>16 (24)</td>
<td>2 (3)</td>
<td>18 (27)</td>
</tr>
<tr>
<td>Transient neuropsychiatric events</td>
<td>10 (15)</td>
<td>0</td>
<td>10 (15)</td>
</tr>
<tr>
<td>Tumor lysis syndrome</td>
<td>3 (4)</td>
<td>0</td>
<td>3 (4)</td>
</tr>
</tbody>
</table>

Adapted from Food and Drug Administration (n.d.; 2017). 64,65

a Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care.

b Life-threatening consequences; urgent intervention indicated.

Subsection Summary: B-Cell Acute Lymphoblastic Leukemia

Observed outcomes in a 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 83% response rate (measured by CR
or CRi) seen in the pivotal single-arm trial of tisagenlecleucel in patients with relapsed or refractory acute lymphoblastic leukemia 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 (63%) of the patients and approximately 40% had an adverse event at grade 4 or higher. Long-term follow-up and real-world evidence are required to assess the generalizability of tisagenlecleucel efficacy and safety outside of a clinical trial setting.

**Diffuse Large B-Cell Lymphoma**

The pivotal trial phase 2 single-arm, multicenter trial (JULIET; NCT02445248) enrolled 160 patients with relapsed or refractory DLBCL. Trial results have not been published; data were obtained from the FDA prescribing label.17 Tables 4 and 5 summarize study characteristics and results.

**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>
<th>FU, mo</th>
</tr>
</thead>
</table>
| Novartis17; JULIET (NCT02445248) | Single prospective cohort | Multiple | NR | • Inclusion: Patients with relapsed or refractory DLBCL, who received ≥2 lines of chemotherapy, including rituximab and anthracyline, or relapsed following HCT  
• Exclusion: Active CNS malignancy, prior allogenic HCT, ECOG Performance Status ≥2, CrCl <60 L/min, ALT >5 times normal, cardiac ejection fraction <45%, or absolute lymphocyte concentration <300/μL  
• Total N=160  
  o No receiving US tisagenlecleucel: 92  
  o Excluded: 4  
  o No evidence of disease at baseline: 8,  
  o No baseline imaging: 15  
  o Misclassification of a neuroendocrine tumor as DLBCL: 1  
• Included and analyzed: | Two to 11 d after completing lymphodepleting chemotherapy, tisagenlecleucel administered as a single intravenous infusion | 9.4 (95% CI 7.9 to 10.8) |
ALAT: 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 of Key Pivotal Trial Results

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>ORR&lt;br&gt;%</th>
<th>CRR</th>
<th>PRR</th>
<th>DOR for Responders</th>
<th>DOR if BOR is CR, mo</th>
<th>DOR if BOR is PR, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novartis&lt;sup&gt;17&lt;/sup&gt;; JULIET (NCT02445248)</td>
<td>68</td>
<td>68</td>
<td>68</td>
<td>34</td>
<td>22</td>
<td>12</td>
</tr>
<tr>
<td>Tisagenlecleucel</td>
<td>34 (50)</td>
<td>22 (32)</td>
<td>12 (18)</td>
<td>Not estimable&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>Not estimable</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Values are n (%) (95% CI).

<sup>a</sup> ORR is sum of CRs and PRs.

<sup>b</sup> Among all responders, DOR measured from date of first objective response to date of progression or death from relapse.

<sup>c</sup> Kaplan-Meier estimate in months.

Of the 160 patients enrolled in the study, 68 patients were retrospectively identified and analyzed for the major efficacy outcome. Table 4 summarizes the reasons for exclusion of 24 patients. The prespecified primary efficacy endpoint was ORR based on Lugano criteria<sup>68</sup> 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. The median time to first response to tisagenlecleucel (CR or partial response) was 0.9 months (range, 0.7-3.3 months). The median duration of response was not reached. Response durations were longer in patients who achieved CR, as compared with patients with a best response of partial response. Of the 22 patients who experienced a CR, 9 achieved this status by 1 month, 12 more by month 3, and the last by month 6 after tisagenlecleucel infusion. 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).<sup>69</sup>

Safety
Table 6 summarizes safety data assessed for 106 patients treated with tisagenlecleucel.

Table 6. Summary of Adverse Events Reported in >20% of Patients in the Pivotal Study (N=106)

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>All Grades, %</th>
<th>Grade ≥3, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokine release syndrome</td>
<td>74</td>
<td>23</td>
</tr>
<tr>
<td>Infections</td>
<td>42</td>
<td>25</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>34</td>
<td>6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>31</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>Hypotension (includes hypotension and orthostatic hypotension)</td>
<td>26</td>
<td>8</td>
</tr>
<tr>
<td>Fatigue (includes fatigue and malaise)</td>
<td>26</td>
<td>7</td>
</tr>
</tbody>
</table>
Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>All Grades, %</th>
<th>Grade ≥3, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema\textsuperscript{a}</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td>Headache (includes headaches and migraines	extsuperscript{1})</td>
<td>21</td>
<td>0</td>
</tr>
</tbody>
</table>

Adapted from Novartis Pharmaceuticals (2018).\textsuperscript{17}

\textsuperscript{a} Edema includes face edema, generalized edema, localized edema, edema peripheral, and peripheral swelling.

\textbf{Subsection Summary: Diffuse Large B-Cell Lymphoma}

Observed outcomes in a 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 high response rate (measured by CR/CRi or CR plus partial response) seen in the pivotal trial of tisagenlecleucel could be the result of 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. CRS was observed in more than half of the patients in the pivotal trial. Long-term follow-up and real-world evidence are required to assess the generalizability of efficacy and safety of tisagenlecleucel outside of a clinical trial setting.

\textbf{Axicabtagene Ciloleucel}

The approval of axicabtagene ciloleucel was based on the results of an open-label, multicenter phase 1/2 study called ZUMA-1, which reported CR rates and duration of response demonstrated in the phase 2 portion of the study. Trial results have not been published; data were obtained from FDA documents and the approved label.\textsuperscript{18,70,71} Adults with aggressive B-cell non-Hodgkin lymphoma that was primary refractory, refractory to a second or greater line of therapy, or relapsed within 1 year after autologous hematopoietic cell transplantation were enrolled in the study. Patients with prior allogeneic hematopoietic cell transplantation, 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 7 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 end point 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. Table 7 summarizes the trial results.
Table 7. Summary of Efficacy Results of the Pivotal Study

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Results, n (%) (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary end point</strong></td>
<td></td>
</tr>
<tr>
<td>Objective remission rate (CR + PR)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>N=101 73 (72) (62 to 81)</td>
</tr>
<tr>
<td>CR</td>
<td>52 (51) (41 to 62)</td>
</tr>
<tr>
<td>PR</td>
<td>21 (21) (13 to 30)</td>
</tr>
<tr>
<td><strong>Secondary end points</strong></td>
<td></td>
</tr>
<tr>
<td>Median duration of response, mo&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>N=73 9.2 (5.4 to NE)</td>
</tr>
<tr>
<td>All patients</td>
<td></td>
</tr>
<tr>
<td>CR only</td>
<td>NE (8.1 to NE)</td>
</tr>
<tr>
<td>PR only</td>
<td>2.1 (1.3 to 5.3)</td>
</tr>
<tr>
<td>Median follow-up for duration of response, mo&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>7.9</td>
</tr>
</tbody>
</table>

Adapted from Kite Pharma (2017)<sup>18</sup>

CR: complete response; NE: not estimable; PR: partial response.

<sup>a</sup> Per 2007 revised International Working Group criteria, as assessed by the independent review committee.

<sup>b</sup> Duration of response was measured from the date of the first objective response to the date of progression or death from relapse or toxicity.

<sup>c</sup> Kaplan-Meier estimates.

**Safety**

Safety data assessed 108 patients treated with axicabtagene ciloleucel. Adverse events of special interest are summarized in Table 8. All patients experienced at least 1 adverse event following infusion and 94% (n=102) experienced grade 3 or higher events. Serious adverse events were observed in 56 (52%) of patients, and serious adverse events that were grade 3 or higher occurred in 48 (44%) patients. Overall, 34 deaths were reported from the time of informed consent to the trial data cutoff (January 27, 2017). Thirty patients died of progressive disease and 4 deaths were attributed to axicabtagene ciloleucel as per FDA analysis, of which 3 occurred within 30 days of infusion.

The median time to onset for CRS was 2 days (range, 1-12 days), and the median time to resolution was 7 days (range, 2-58 days). Forty-five percent (49/108) of patients received tocilizumab for CRS management. The median time to onset of neurologic toxicity was 4 days (range, 1-43 days). The median duration was 17 days. Prolonged encephalopathy lasting up to 173 days was noted. Most common neurologic toxicities included encephalopathy, headache, tremor, dizziness, aphasia, delirium, insomnia, and anxiety. Neurologic toxicities were managed with supportive care and/or corticosteroids. Almost all neurologic toxicities at grade 2 or higher occurred within 7 days following infusion.

Table 8. Summary of Serious Adverse Events of Special Interest in the Pivotal Study (N=108)

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>All Grades, n (%)</th>
<th>Grades ≥3, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokine release syndrome</td>
<td>101 (63)</td>
<td>14 (13)</td>
</tr>
<tr>
<td>Neurologic toxicities&lt;sup&gt;a&lt;/sup&gt;</td>
<td>94 (21)</td>
<td>34 (31)</td>
</tr>
<tr>
<td>Serious infections</td>
<td>41 (38)</td>
<td>25 (23)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>39 (36)</td>
<td>35 (32)</td>
</tr>
<tr>
<td>Prolonged cytopenia not resolved by day 30</td>
<td>-</td>
<td>30 (28)</td>
</tr>
<tr>
<td>Hypogammaglobulinemia</td>
<td>16 (15)</td>
<td>0</td>
</tr>
</tbody>
</table>
Adapted from Food and Drug Administration (2017).\textsuperscript{70} Ninety-eight percent of all neurologic toxicities occurred within first 8 weeks of axicabtagene ciloleucel infusion.

**Subsection Summary: Axicabtagene Ciloleucel**

Observed outcomes in a 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 high response rate (measured by CR/CRi or CR plus partial response) seen in the pivotal trials of axicabtagene ciloleucel could be the result of 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, 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. CRS was observed in more than half of the patients in the pivotal trials and more than 40% of patients had an adverse event at grade 3 or higher. Long-term follow-up 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**

**Cytotoxic T Lymphocytes**

For individuals with Epstein-Barr virus–associated cancers who receive cytotoxic T lymphocytes, the evidence includes 2 small, prospective noncomparative cohort studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The cohort studies have shown a treatment response to infused cytotoxic T lymphocytes directed against cancer-associated viral antigens. To establish efficacy, the following are needed: large, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with *Cytomegalovirus*-associated cancers who receive cytotoxic T lymphocytes, the evidence includes a single case series. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. In the absence of an RCT comparing cytotoxic T lymphocytes with the standard of care, no conclusions can be made. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Cytotoxic-Induced Killer Cells**

For individuals with nasopharyngeal carcinoma who receive CIK cells, the evidence includes a single RCT. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The RCT reported a numerically favorable but statistically insignificant effect on progression-free survival and overall survival. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.
For individuals with renal cell carcinoma who receive CIK cells, the evidence includes multiple RCTs. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The largest of the RCTs reported statistically significant gains in progression-free survival and overall survival with CIK cell–based immunotherapy compared with interleukin-2 plus interferon-α-2. This body of evidence is limited by the context of the studies (non-U.S.) and choice of a nonstandard comparator. The other two RCTs have also reported response rates in favor of CIK therapy with inconsistent effect on survival. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with gastric cancer who receive CIK cells, the evidence includes a single nonrandomized prospective study. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The prospective cohort study reported statistically significant effects on disease-free survival and overall survival in favor of immunotherapy vs no immunotherapy. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with colorectal cancer who receive CIK cells, the evidence includes a single RCT. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Results of the RCT showed a statistically significant effect on overall survival in favor of immunotherapy vs chemotherapy alone. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with hepatocellular carcinoma who receive CIK cells, the evidence includes several RCTs. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Several RCTs from Asia have generally reported some benefits in response rates and/or survival. The results of a meta-analysis of these trials have also shown a statistically significant 41% reduction in the hazard of death, but there was considerable heterogeneity across the included studies. This body of evidence is limited by the context of the studies (non-U.S.), small sample sizes, heterogeneous treatment groups, and other methodologic weaknesses. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with non-small-cell lung cancer who receive CIK cells, the evidence includes multiple RCTs and a systematic review. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. A single systematic review of RCTs reported some benefits in median time to progression and median survival time. The trials assessed in the systematic review were limited by the context of the studies (non-U.S.), small sample sizes, heterogeneous treatment groups, and other methodologic weaknesses. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.
showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Tumor-Infiltrating Lymphocytes**

For individuals with melanoma who receive tumor-infiltrating lymphocytes, the evidence includes a single RCT. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Results of a small RCT have reported no difference in relapse or survival outcomes. Cohort studies in patients with refractory metastatic melanoma have demonstrated response rates of 49% with immunotherapy and 52% to 72% with no immunotherapy. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Dendritic Cells**

For individuals with glioblastoma multiforme who receive dendritic cells, the evidence includes a systematic review of observational studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Because of the observational and noncomparative nature of the available evidence, it is difficult to draw any meaningful conclusions. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. Interim results from one such RCT have been published but are not informative because the patients were unblinded and results combined for the treatment and placebo arms. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with non-small-cell lung cancer who receive dendritic cells, the evidence includes 2 RCTs and a meta-analysis. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The RCTs have generally reported some benefits in response rates and/or survival. The meta-analysis of these trials also reported a statistically significant reduction in the hazard of death. Most trials were from Asia and did not use the standard of care as the control arm. This body of evidence is limited by the context of the studies (non-U.S.), small sample sizes, heterogeneous treatment groups, and other methodologic weaknesses. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with medullary thyroid cancer who receive dendritic cells, the evidence includes 1 prospective noncomparative study. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. A small prospective noncomparative study in 10 medullary thyroid cancer patients treated with autologous dendritic cells has been published. There are no RCTs comparing dendritic cell–based adoptive immunotherapy with the standard of care and, therefore, no conclusions can be made. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.
For individuals with pancreatic cancer who receive dendritic cells, the evidence includes a small prospective noncomparative study. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The study reported on treatment outcomes for 5 patients with pancreatic cancer. Because of the noncomparative nature of the available evidence and small sample base, it is difficult to draw any meaningful conclusions. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Genetically Engineered T Cells**

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

**Tisagenlecleucel**
For individuals who are up to 25 years of age with relapsed or refractory B-cell acute lymphoblastic leukemia who receive tisagenlecleucel, the evidence includes multiple single-arm prospective trials. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The pivotal single-arm trials reported an 83% response rate (measured by complete response or complete remission with incomplete blood count) in heavily pretreated patients. All patients who achieved a complete remission or complete remission with incomplete blood count were also minimal residual disease-negative, which is predictive of survival in acute lymphoblastic leukemia patients. After a median follow-up of 4.8 months, the median duration of response was not reached. The observed benefits seen with tisagenlecleucel were offset by a high frequency and severity of adverse events. Cytokine release syndrome was observed in more than half (63%) of the patients, and approximately 40% had an adverse event at grade 4 or higher. Long-term follow-up and real-world evidence are required to assess the generalizability of tisagenlecleucel efficacy and safety outside of the clinical trial setting. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are adults with a histologically confirmed diagnosis of aggressive non-Hodgkin lymphoma (eg, diffuse large B-cell lymphoma not otherwise specified, high-grade B-cell lymphoma, transformed follicular lymphoma) who receive tisagenlecleucel, the evidence includes a single-arm prospective trial. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The pivotal single-arm trial reported a 50% overall response rate (measured by complete or partial remission) in heavily pretreated patients. After a median follow-up of 9.4 months, the median duration of response was not reached. The observed benefits were offset by a high frequency and severity of adverse events. Any grade cytokine release syndrome was observed.
in 74% of the patients, and 23% had grade 3 or higher cytokine release syndrome. Long-term follow-up and real-world evidence are required to assess the generalizability of tisagenlecleucel efficacy and safety outside of the clinical trial setting. The manufacturer has agreed to a postmarketing requirement observational registry study to collect safety information for patients treated with the marketed product. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Axicabtagene Ciloleucel**
For individuals who are adults with a histologically confirmed diagnosis of aggressive non-Hodgkin lymphoma (eg, diffuse large B-cell lymphoma not otherwise specified, high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, transformed follicular lymphoma) who receive axicabtagene ciloleucel, the evidence includes a single-arm prospective trial. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The pivotal single-arm trial reported a 72% overall response rate (measured by complete or partial remission) in heavily pretreated patients. After a median follow-up of 7.9 months, the median duration of response was 9.2 months. The observed benefits were offset by a high frequency and severity of adverse events. Cytokine release syndrome was observed in more than half (63%) of the patients, and 44% had an adverse event at grade 3 or higher. Long-term follow-up and real-world evidence are required to assess the generalizability of axicabtagene ciloleucel efficacy and safety outside of the clinical trial setting. The manufacturer has agreed to a postmarketing requirement observational registry study to collect safety information for patients treated with the marketed product. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**SUPPLEMENTAL INFORMATION**

**PRACTICE GUIDELINES AND POSITION STATEMENTS**
Current guidelines from the National Comprehensive Cancer Network do not include recommendations for adoptive immunotherapy to treat cancers of the bladder, central nervous system, head and neck, hepatobiliary system, kidney, pancreatic, stomach, or thyroid, melanoma, Hodgkin lymphoma, or non-small-cell lung cancer. Current National Comprehensive Cancer Network guidelines for acute lymphoblastic leukemia recommend (category 2A) tisagenlecleucel as a treatment option for:

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

Current Network guidelines for B-cell lymphomas recommend (category 2A) axicabtagene ciloleucel or tisagenlecleucel as a treatment option:

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

**U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS**
Not applicable.
MEDICARE NATIONAL COVERAGE
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

ONGOING AND UNPUBLISHED CLINICAL TRIALS
Some currently unpublished trials that might influence this review are listed in Table 9.

Table 9. 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>NCT02118415</td>
<td>Targeted Natural Killer (NK) Cell Based Adoptive Immunotherapy for the Treatment of Patients With Non-Small Cell Lung Cancer (NSCLC) After Radiochemotherapy (RCT)</td>
<td>90</td>
<td>Feb 2018 (ongoing)</td>
</tr>
<tr>
<td>NCT02229266</td>
<td>Randomised Controlled Phase-2 Trial to Determine the Efficacy of Adoptive Immunotherapy With NK Cells in High-risk AML (HINKL)</td>
<td>56</td>
<td>Sep 2019</td>
</tr>
<tr>
<td>NCT01993719</td>
<td>A Phase II Prospective Randomized Study of Cell Transfer Therapy for Metastatic Melanoma Using Tumor Infiltrating Lymphocytes Plus IL-2 Comparing Two Different Chemotherapy Preparative Regimens</td>
<td>120</td>
<td>Sep 2019</td>
</tr>
<tr>
<td>NCT01966289</td>
<td>SGI-110 in Combination With an Allogeneic Colon Cancer Cell Vaccine (GVAX) and Cyclophosphamide (CY) in Metastatic Colorectal Cancer (mCRC)</td>
<td>32</td>
<td>Dec 2019</td>
</tr>
<tr>
<td>NCT01319565</td>
<td>Prospective Randomized Study of Cell Therapy for Metastatic Melanoma Using Short-Term Cultured Tumor Infiltrating Lymphocytes Plus IL-2 Following Either a Non-Myeloablative Lymphocyte Depleting Chemotherapy Regimen Alone or in Conjunction w/1200 TBI</td>
<td>102</td>
<td>Jun 2020</td>
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<tr>
<td>NCT02278887</td>
<td>Study Comparing TIL to Standard Ipilimumab in Patients With Metastatic Melanoma (TiL)</td>
<td>162</td>
<td>Sep 2020</td>
</tr>
<tr>
<td>NCT00338377a</td>
<td>Lymphodepletion Plus Adoptive Cell Transfer With or Without Dendritic Cell Immunization</td>
<td>189</td>
<td>Feb 2019</td>
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<tr>
<td>NCT01204684</td>
<td>Dendritic Cell Vaccine for Patients With Brain Tumors</td>
<td>60</td>
<td>Oct 2019</td>
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<tr>
<td>NCT01691625a</td>
<td>Concurrent Chemoradiation With or Without DC-CKI Immunotherapy in Treating Locally Advanced Esophageal Cancer</td>
<td>50</td>
<td>Sep 2019</td>
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<tr>
<td>NCT02445248</td>
<td>Study of Efficacy and Safety of CTL019 in Adult DLBCL Patients</td>
<td>130</td>
<td>Jan 2024</td>
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<tr>
<td>NCT02228096</td>
<td>Study of Efficacy and Safety of CTL019 in Pediatric ALL Patients</td>
<td>67</td>
<td>Oct 2024</td>
</tr>
<tr>
<td>NCT02445222</td>
<td>CD19 CART Long Term Follow Up (LTFU) Study</td>
<td>500</td>
<td>Sep 2036</td>
</tr>
</tbody>
</table>
### Adoptive Immunotherapy

#### NCT No. | Trial Name | Planned Enrollment | Completion Date
--- | --- | --- | ---
Axicabtagene ciloleucel
NCT02601313 | A Phase 2 Multicenter Study Evaluating Subjects With Relapsed/Refractory Mantle Cell Lymphoma (ZUMA-2) | 70 | Jul 2018
NCT02614066 | A Study Evaluating KTE-C19 in Adult Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (r/r ALL) (ZUMA-3) (ZUMA-3) | 75 | Mar 2019
NCT02625480 | A Multi-Center Study Evaluating KTE-C19 in Pediatric and Adolescent Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ZUMA-4) | 75 | Jul 2019
NCT03105336 | A Phase 2 Multicenter Study of Axicabtagene Ciloleucel in Subjects With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma (ZUMA-5) | 50 | Jul 2023

NCT: national clinical trial.

*a* Denotes industry-sponsored or cosponsored trial.

### REFERENCES


**CODES**

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>36511</td>
<td>Therapeutic apheresis; for white blood cells</td>
</tr>
<tr>
<td></td>
<td>37799</td>
<td>Unlisted procedure, vascular surgery (therapeutic leukapheresis)</td>
</tr>
<tr>
<td></td>
<td>38999</td>
<td>Unlisted procedure, hemic or lymphatic system</td>
</tr>
<tr>
<td></td>
<td>96365</td>
<td>Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to one hour</td>
</tr>
<tr>
<td>HCPCS</td>
<td>S2107</td>
<td>Adoptive immunotherapy, ie, development of specific antitumor reactivity (eg, tumor-infiltrating lymphocyte therapy) per course of treatment</td>
</tr>
<tr>
<td></td>
<td>C9399; Q2040</td>
<td>Unclassified drugs or biological- Use for Kymriah and Yescarta Tisagenlecleucel, up to 250 million car-positive viable T cells, including leukapheresis and dose preparation procedures, per infusion (new code 01/01/18)</td>
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<tr>
<td>ICD-10-CM</td>
<td>C00.0-C96.9</td>
<td>Investigational for all diagnoses</td>
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<td>ICD-10-PCS</td>
<td></td>
<td>ICD-10-PCS codes are only used for inpatient services. There is no specific ICD-10-PCS code for this therapy.</td>
</tr>
<tr>
<td></td>
<td>6A550Z1</td>
<td>Extracorporeal therapies physiological systems, pheresis, circulatory, single, leukocytes</td>
</tr>
<tr>
<td></td>
<td>6A551Z1</td>
<td>Extracorporeal therapies physiological systems, pheresis, circulatory, multiple, leukocytes</td>
</tr>
<tr>
<td></td>
<td>XW033C3; XW043C3</td>
<td>New technology codes for Engineered Autologous Chimeric Antigen Receptor</td>
</tr>
</tbody>
</table>
**Adoptive Immunotherapy**

<table>
<thead>
<tr>
<th>Type of service</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Place of service</td>
<td>Inpatient/Outpatient</td>
</tr>
</tbody>
</table>

**T-cell Immunotherapy, peripheral vein and central vein codes**

**POLICY HISTORY**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/11/14</td>
<td>Replace policy</td>
<td>Policy updated with literature review through November 2, 2014; references 6-9, 12, 14-17, 41, 46, 52-53, and 56-65 added; reference 55 updated. Rationale reorganized and references renumbered. Cytotoxic T-lymphocytes and genetically engineered T-cells added to investigational policy statements; “autologous” added to clarify antigen-loaded dendritic cells.</td>
</tr>
<tr>
<td>12/10/15</td>
<td>Replace policy</td>
<td>Policy updated with literature review through November 10, 2015; references 13 and 17-18 added. Section on lymphokine-activated killer cell deleted due obsolete intervention. Policy statements unchanged.</td>
</tr>
<tr>
<td>02/24/17</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho annual review; no change to policy.</td>
</tr>
<tr>
<td>10/12/17</td>
<td>Replace policy</td>
<td>Policy updated with literature review through April 25, 2017, and FDA documents accessed subsequent to this date; references 3-10, 23-24, 55-58, and 70 were added. Rationale reorganized and section on tisagenlecleucel was added. Policy statements changed to add tisagenlecleucel as medically necessary.</td>
</tr>
<tr>
<td>01/30/18</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho adopted changes as noted, effective 04/30/2018. Policy updated with literature review through November 6, 2017, and FDA documents accessed subsequent to this date; references 12-18 and 67-68 added. Rationale reorganized and section on axicabtagene ciloleucel was added. Policy statements changed to add axicabtagene ciloleucel as medically necessary.</td>
</tr>
<tr>
<td>03/23/18</td>
<td>Coding update only</td>
<td>Blue Cross of Idaho removed unlisted code C9399, and added Q2041 to be used for YESCARTA.</td>
</tr>
<tr>
<td>04/30/18</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho adopted changes as noted, effective 07/30/2018. Policy statement clarified, changing “2 or 3” to “3”, to read: “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)”</td>
</tr>
<tr>
<td>07/25/18</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho adopted change as noted, effective 10/30/2018. Policy updated with literature review through June 14, 2018; several references added. Tisagenlecleucel added to the PICO table, and the second medically policy statement with modified criteria.</td>
</tr>
</tbody>
</table>