Adoptive immunotherapy, using adoptive cellular therapy for the administration of cytotoxic T lymphocytes, cytokine-induced killer cells, tumor-infiltrating lymphocytes, antigen-loaded autologous dendritic cells, or genetically engineered T cells is considered investigational.

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 (greater than or equal to 5% lymphoblasts)
- Are 25 years old or younger 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 four 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 six weeks prior to tisagenlecleucel infusion
  - Active central nervous system disease
  - Patients with central nervous system 2 disease (cerebrospinal fluid containing blasts, but less than 5 white blood cells per microliter) are eligible

Other applications of adoptive immunotherapy are considered investigational.

\(^a\) 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, i.e., failure to eradicate all detectable leukemia cells (less than 5% blasts) from the bone marrow and blood with subsequent restoration of normal hematopoiesis (greater than 25% marrow cellularity and normal peripheral blood counts).

**Policy Guidelines**

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

The recommended dosage of tisagenlecleucel for patients 50 kg or less is 0.2 to 5.0\(\times 10^6\) chimeric antigen receptor-positive viable T cells per kg body weight intravenously; for patients above 50 kg, dose is 0.1 to 2.5 \(\times 10^8\) total chimeric antigen receptor-positive viable T cells (non-weight-based) intravenously.

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

- **CNS 1:** Absence of blasts on cerebrospinal fluid cytospin preparation, regardless of the white blood cell (WBC) count
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- **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 (e.g., facial nerve palsy, brain/eye involvement, hypothalamic syndrome)

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

Tisagenlecleucel is available only through a restricted program under a risk evaluation and mitigation strategy (REMS) called the Kymriah REMS. The requirement for the REMS components are as follows:
- Health care facilities that dispense and administer tisagenlecleucel must be enrolled and comply with the REMS requirements
- Certified health care facilities must have onsite, immediate access to tocilizumab, and ensure that a minimum of 2 doses of tocilizumab are available for each patient for administration within 2 hours after tisagenlecleucel infusion, if needed for treatment of cytokine release syndrome
- Certified health care facilities must ensure that health care providers who prescribe, dispense or administer tisagenlecleucel are trained about the management of cytokine release syndrome and neurologic toxicities

**Description**

The spontaneous regression of certain cancers (e.g., renal cell carcinoma, melanoma) supports the idea that a patient's immune system can delay tumor progression and, on rare occasions, can eliminate tumors altogether. These observations have led to research into various immunologic therapies designed to stimulate a patient’s own immune system. Adoptive immunotherapy is a method of activating lymphocytes and/or other types of cells for the treatment of cancer and other diseases. Cells are removed from the patient, processed for some period of time, and then infused back into the patient.

**Related Policies**

- Cellular Immunotherapy for Prostate Cancer

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates [e.g., Federal Employee Program (FEP)] prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of the FDA-approved technologies on the basis of medical necessity alone.

**Regulatory Status**

Adoptive immunotherapy is not a U.S. Food and Drug Administration–regulated procedure.
On August 30, 2017, tisagenlecleucel (Kymriah™; Novartis) was approved by the Food and Drug Administration for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse.

**Rationale**

**Background**

**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 (IL-2) and other cytokines. More recent techniques have yielded select populations of cytotoxic T lymphocytes with specific reactivity to tumor antigens. Peripheral lymphocytes are propagated in vitro with antigen-presenting dendritic cells that have been pulsed with tumor antigens. Alternatively, innate tumor-infiltrating lymphocytes (TIL) from the tumor biopsy are propagated in vitro with IL-2 and anti-CD3 antibody, a T-cell activator. Expansion of TIL for clinical use is labor intensive and requires laboratory expertise. Only a few cancers are infiltrated by T cells in significant numbers; of these, TIL can be expanded in only approximately 50% of cases. These factors limit the widespread applicability of TIL treatment. Recently, cytokine-induced killer cells have been recognized as a new type of 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.¹

**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) anti-tumor lymphocytes following a lymphodepletive preparative regimen.”²

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 (i.e., 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 Blue Shield of California Medical Policy: Cellular Immunotherapy for Prostate Cancer for a discussion of dendritic cell-based immunotherapy for prostate cancer.)
In an attempt to regulate the host immune system further, recent protocols use various cytokines (e.g., IL-7 and IL-15 instead of IL-2) to propagate lymphocytes. Protocols also differ in the extent of host lymphodepletion induced prior to transfusing lymphocytes to the tumor-bearing host.

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.

**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 blast cells displace the normal hematopoietic bone marrow and cause cytopenias in all 3 cell lineages (anemia, thrombocytopenia, granulocytopenia). Leukostasis affecting brain and lung may also occur. Death occurs commonly due to severe pancytopenia and resulting infections. Refractory (resistant) disease is defined as those patients who fail to obtain complete response with induction therapy, i.e., failure to eradicate all detectable leukemia cells (<5% blasts) from the bone marrow and blood with subsequent restoration of normal hematopoiesis (>25% marrow cellularity and normal peripheral blood counts). Relapsed disease describes the reappearance of leukemia cells in the bone marrow or peripheral blood after the attainment of a complete remission. Minimal residual disease (MRD) refers to the presence of disease in cases deemed to be in complete remission by conventional pathologic analysis. MRD positivity is defined as the presence of 0.01% or more ALL cells and has been shown to be a strongest prognostic factor to predict the risk of relapse and death when measured during and after induction therapy in both newly diagnosed and relapsed ALL. In a 2017 meta-analysis of 20 studies of 11,249 pediatric ALL, the hazard ratio for event-free survival in MRD-negative patients compared with MRD-positive patients was 0.23 (95% confidence interval, 0.18 to 0.28).

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. It is largely a disease of the young with approximately 60% of cases occurring in patients younger than 20 years old with a median age at diagnosis of 15 years. While it is treatable in 85% cases, approximately 15% of children and young adults with ALL will relapse while 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 approved clofarabine (as a single agent or in combination) in 2004 and blinatumomab in 2014 for relapsed and refractory ALL. Reported median objective response rates in the pivotal trials of the 2 agents were 19.7% and 33%, the median durations of response was 2.5 months and 6 months, and median overall survival durations were 3 months and 7.5 months, respectively. 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.

**Tisagenlecleucel**

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

**Literature Review**

Assessment of efficacy for therapeutic intervention involves a determination of whether an intervention improves health outcomes. The optimal study design for this purpose is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. Intermediate outcome measures, also known as surrogate outcome measures, may also be adequate if there is an established link between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes provide useful information on health outcomes but are prone to biases such as non-comparability of treatment groups, placebo effect, and variable natural history of the condition.

Adoptive immunotherapy has been investigated for the treatment of relatively common cancers in which novel treatments have been adopted when randomized clinical trials show efficacy. The selected studies included only new randomized clinical trials.

**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, and postoperative hepatocellular carcinoma.

**Renal Cell Carcinoma**

**Cytotoxic T Lymphocytes**

Bollard et al (2014) conducted an international prospective cohort study of cytotoxic T lymphocytes (CTL) therapy in patients with Epstein-Barr virus (EBV)—positive Hodgkin or non-Hodgkin lymphoma. 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. 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. 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 non-hematologic toxicities were not observed during CTL therapy. In a 2014 Japanese series of 7 patients who received CTLs for advanced oral and maxillofacial cancers, 1-year survival in patients who achieved response (n=3) and in those with progressive disease (n=4) were 100% and 25%, respectively, although definitions of response were unclear.

**Subsection Summary: Epstein-Barr Virus–Associated Cancers**

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

**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 indicates 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 is needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit.

**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 up 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 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 <0.001, respectively). Median PFS and OS in arm 1 were significantly longer than those in arm 2 (PFS, 12 vs 8 months, p=0.024; OS, 46 vs 19 months, p<0.001). 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% 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 with 20 patients who had unilateral, locally
advanced renal cell carcinoma after nephrectomy.20 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% vs 50% in
the CIK and control groups, respectively; 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.21 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 better in the CIK group (p=0.021). Among the 62 inoperable
patients, OS was better 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 gain in PFS and OS with CIK
cell immunotherapy compared with interleukin-2 (IL-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
remaining 2 RCTs also reported response rate in favor of CIK therapy with inconsistent effect on
survival. To establish efficacy, the following is needed: larger, well-conducted, multicentric trials
with adequate randomization procedures, blinded assessments, centralized oversight, and the
use of an appropriate standard of care as the control arm showing treatment benefit.

Gastric Cancer
In 2012, Shi et al 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.22 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 is needed: larger, well-conducted, multicentric trials with
adequate randomization procedures, blinded assessments, centralized oversight, and the use of
an appropriate standard of care as the control arm showing treatment benefit.

Colorectal Cancer
Zhao et al (2016) reported the results of a controlled trial in which 122 patients with metasta
colorectal cancer were randomized to CIK cell immunotherapy plus chemotherapy (n=61) or
chemotherapy alone (n=61).23 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 is needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit.

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).24 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 meta-analysis reported a statistical 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 hepatocellular carcinoma.25 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. 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 2014 nonrandomized study from China 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).26

Lee et al (2015) conducted an RCT in Korea of 230 patients being treated for hepatocellular carcinoma by surgical resection, radiofrequency ablation, or percutaneous ethanol injection.27 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 hepatocellular cancers. These studies have generally reported some benefits in response rates and/or survival. Results of meta-analysis of these trials also reported a statistical 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 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 is needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments,
centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit.

**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 dendritic cell therapy. All were conducted in China. A significant effect of CIK was found for 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 is needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit.

**Tumor-Infiltrating Lymphocytes**

**Melanoma**

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 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.

**Subsection Summary: Melanoma**

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 the majority of patients who achieved CR were observed beyond 3 years. Toxicities appeared primarily associated with myeloablative regimen. Larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and use of 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,33 myeloma,34,35 subcutaneous tumors,36 melanoma,37 NSCLC,38,39 renal cell cancer,40 and cervical cancer.41 A 2012 systematic review highlighted progress in dendritic cell–based immunotherapy in epithelial ovarian cancer.42

**Glioblastoma Multiforme**
In 2013, Bregy et al published a systematic review of observational studies of active immunotherapy using ADCs in the treatment of glioblastoma multiforme.43 Twenty-one studies published through early 2013 were included in this review (total N=403 patients). Vaccination with dendritic cells 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%).

**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 is subject to publication and selection bias, which has the potential to lessen or amplify the true potential of adoptive immunotherapy. To establish efficacy, the following is needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit.

**Non-Small-Cell Lung Cancer**
Shi et al (2012) conducted an RCT at a university cancer center in China to evaluate the role of dendritic cell (DC)/CIK combination immunotherapy as maintenance treatment of advanced NSCLC.38 From 2008 to 2010, 60 patients with stage III or IV disease after treatment with 4 cycles of a platinum-based chemotherapy regimen were randomly divided into 2 groups. One group was treated with DC/CIK cell therapy (n=30), and the other was a control group who received no adoptive immunotherapy (n=30). Outcome measures were PFS and adverse events of treatment/toxicity. PFS was 3.2 months in the DC/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/CIK group, including bone marrow toxicity and gastrointestinal reactions. The findings of this small single-center RCT indicate that combination immunotherapy with dendritic cells 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 DC/CIK combination immunotherapy with any other treatment (placebo, no intervention, conventional treatment, or other complementary and alternative medicines) for any cancer type and stage.44 Two included RCTs that compared DC/CIK plus chemotherapy with chemotherapy alone in patients with stage III or IV NSCLC reported OS estimates (total N=150). Pooled relative risk (RRs) favored DC/CIK therapy at 2 years but not at 1 year (RR for 1-year OS=1.38; 95% CI, 1.00 to 1.90; p=0.05; I²=5%; RR 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.28

**Subsection Summary: Non-Small-Cell Lung Cancer**

Two RCTs and a meta-analysis of these RCTs have evaluated the efficacy of DC/CIK cells in NSCLC. The RCTs have generally reported some benefits in response rates and/or survival. Results of meta-analysis of these trials also reported a statistical significant reduction in the hazard of death. However, the effect was inconsistent. Most were from Asia and did not use standard of care as 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 is needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit.

**Medullary Thyroid Cancer**

In a 2009 phase 1 pilot study, 10 patients with metastatic medullary thyroid cancer (MTC) were treated with ADCs pulsed with allogeneic MTC tumor cell lysate.45 At 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 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 with treated with ADCs has been published. There are no RCTs comparing dendritic cell-based adoptive immunotherapy with standard of care and therefore no conclusions can be made. To establish efficacy, the following is needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit.

**Pancreatic Cancer**

A 2009 phase 1 study of 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.46 One patient had a partial response, two had stable disease for more than 6 months, and 2 patients 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 dendritic cell-based adoptive immunotherapy with standard of care and therefore no conclusions can be made. To establish efficacy, the following is needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight and the use of an appropriate standard of care as the control arm showing treatment benefit.

**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.47-49
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).50 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 complete response 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 (e.g., prostate, ovary, breast, thyroid) or are not expressed on normal adult tissues (e.g., cancer-testes antigens).

Additional studies have examined TCR gene therapy in Hodgkin51 and non-Hodgkin lymphoma,50 prostate tumors,53 and neuroblastoma.54

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 Pivotal Trial
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. This trial has not been published; information was obtained from the Food and Drug Administration 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 patient who achieved objective remission rate (ORR; 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% confidence intervals for ORR was greater than 20%. The key secondary outcome was proportion of patients who achieve best ORR (CR or CRi with an 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 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 Kamofsky/Lansky Performance Status score was 90 (range, 50-100), 79% had relapsed disease, 12% had chemotherapy 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 shows 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 six received hematopoietic cell transplant, five received a new cancer therapy, and one 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, four died (three after disease relapse, one after new cancer therapy was initiated while in remission).

Table 1. Summary of Efficacy Results of the Pivotal Study

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Results, n (%) (95% confidence interval) or %</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>63</td>
</tr>
<tr>
<td><strong>Primary end point (3 mo)</strong></td>
<td></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-negative)</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>
<tr>
<td>Percent relapse-free at 6 mo after remission</td>
<td>75</td>
</tr>
<tr>
<td>Percent survival at 6 mo</td>
<td>89</td>
</tr>
<tr>
<td>Percent survival at 9 mo</td>
<td>79</td>
</tr>
<tr>
<td>Percent survival at 12 mo</td>
<td>79</td>
</tr>
</tbody>
</table>

CR: Complete Remission; CRi: Complete Remission with Incomplete Blood Count Recovery; MRD: Minimal Residual Disease.

Supportive Studies
Two single-arm studies that included a total of 84 patients were conducted using product manufactured at University of Pennsylvania cell and vaccine production facility. The first study was a phase 1/2a single-center study in 55 patients enrolled between March 2012 and November 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 to 37.8 months). 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 August 2014 and February 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. 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.
The Food and Drug Administration also noted infection as a special adverse event of interest. In the first 8 weeks after infusion, 43% (29/68) of patients developed 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 were 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>

* 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>28 (41)</td>
<td>62 (91)</td>
</tr>
<tr>
<td>Cytokine release syndrome</td>
<td>14 (21)</td>
<td>18 (27)</td>
<td>53 (78)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>23 (34)</td>
<td>2 (3)</td>
<td>25 (37)</td>
</tr>
<tr>
<td>Hematopoietic cytopenia not resolved by day 28</td>
<td>10 (15)</td>
<td>12 (18)</td>
<td>25 (37)</td>
</tr>
<tr>
<td>Infections</td>
<td>16 (24)</td>
<td>2 (3)</td>
<td>29 (43)</td>
</tr>
<tr>
<td>Transient neuropsychiatric events</td>
<td>10 (15)</td>
<td>0</td>
<td>30 (44)</td>
</tr>
<tr>
<td>Tumor lysis syndrome</td>
<td>3 (4)</td>
<td>0</td>
<td>3 (4)</td>
</tr>
</tbody>
</table>

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

* Life-threatening consequences; urgent intervention indicated.
**Subsection Summary: Tisagenlecleucel**

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 is required to assess the generalizability of tisagenlecleucel efficacy and safety 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 is 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 standard of care, no conclusions can be made. To establish efficacy, the following is needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

**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 is needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 2 RCTs have also reported response rates in favor of CIK therapy with inconsistent effect on survival. To establish efficacy, the following is needed: larger, well-conducted, multicentric trials with adequate
randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 effect on disease-free survival and overall survival in favor of immunotherapy vs no immunotherapy. To establish efficacy, the following is needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 is needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 is needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 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 is needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

**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 is needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit.
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 is needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 results of a meta-analysis of these trials also reported a statistical significant reduction in the hazard of death. Most trials were from Asia and did not use standard of care as the control arm. This body of evidence is limited by the context of the studies (non-U.S.), small sample sizes, heterogeneous treatment groups, and other methodologic weaknesses. To establish efficacy, the following is needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with medullary thyroid cancer who receive dendritic cells, the evidence includes one 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 standard of care and, therefore, no conclusions can be made. To establish efficacy, the following is needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 is needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Genetically Engineered T Cells**

**Peripheral Lymphocytes**

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

**Tisagenlecleucel**

For individuals who are 3 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 reactions. Cytokine release syndrome was observed in more than half (63%) of the patients, and approximately 40% had an adverse event at grade 4 or higher. Long-term follow-up and real-world evidence is required to assess the generalizability of tisagenlecleucel efficacy and safety outside of a clinical trial setting. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**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, thyroid, melanoma, Hodgkin lymphoma or non-small-cell lung cancer.

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

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

**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 4.

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02227641</td>
<td>Preventative/Preemptive Adoptive Transfer of Peptide Stimulated CMV/EBV Specific T-cells in Patients After Allogeneic Stem Cell Transplantation</td>
<td>50</td>
<td>Mar 2017 (ongoing)</td>
</tr>
<tr>
<td>NCT02118415</td>
<td>Targeted Natural Killer (NK) Cell Based Adoptive Immunotherapy for the Treatment of Patients With Non-</td>
<td>90</td>
<td>Feb 2018</td>
</tr>
</tbody>
</table>
### Tumor-infiltrating lymphocytes

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tbody>
<tr>
<td>NCT01995344</td>
<td>Randomised Controlled Phase-2 Trial to Determine the Efficacy of Adoptive Immunotherapy With NK Cells in High-risk AML (HINKL)</td>
<td>90</td>
<td>Dec 2018</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>Prospective Randomized Study of Cell Therapy for Metastatic Melanoma Using Short-Term Cultured Tumor Infiltrating Lymphocytes Plus IL-2 Following Either a Non-Myeloablative Lymphocyte Depleting Chemotherapy Regimen Alone or in Conjunction w/1200 TBI</td>
<td>102</td>
<td>Jun 2020</td>
</tr>
<tr>
<td>NCT02278887</td>
<td>Study Comparing TIL to Standard Ipilimumab in Patients With Metastatic Melanoma (TIL)</td>
<td>162</td>
<td>Sep 2020</td>
</tr>
</tbody>
</table>

### Autologous dendritic cells

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00045968a</td>
<td>Study of a Drug [DCVax®-L] to Treat Newly Diagnosed GBM Brain Cancer</td>
<td>348</td>
<td>Nov 2016 (ongoing)</td>
</tr>
<tr>
<td>NCT01204684</td>
<td>Dendritic Cell Vaccine for Patients With Brain Tumors</td>
<td>60</td>
<td>Sep 2017</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>
</tr>
</tbody>
</table>

### Dendritic cells/cytokine-induced killer cells

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02229266</td>
<td>Small Cell Lung Cancer (NSCLC) After Radiochemotherapy (RCT)</td>
<td>56</td>
<td>Sep 2019</td>
</tr>
<tr>
<td>NCT01999344</td>
<td>TIL Therapy in Metastatic Melanoma and IL2 Dose Assessment (METILDA)</td>
<td></td>
<td></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>
</tr>
<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>
</tbody>
</table>

NCT: National Clinical Trial.  
a Denotes industry-sponsored or cosponsored trial.

### References


Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

MN/IE

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria...
are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</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</td>
</tr>
<tr>
<td></td>
<td>96365</td>
<td>Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour</td>
</tr>
<tr>
<td></td>
<td>Q2040</td>
<td>Tisagenlecleucel, up to 250 million CAR-positive viable T cells, including leukapheresis and dose preparation procedures, per infusion (Code effective 1/1/2018)</td>
</tr>
<tr>
<td></td>
<td>Q2041</td>
<td>Axicabtagene ciloleucel, up to 200 million autologous anti-CD19 CART cells, including leukapheresis and dose preparation procedures, per infusion (Code effective 4/1/2018)</td>
</tr>
<tr>
<td>HCPCS</td>
<td>S2107</td>
<td>Adoptive immunotherapy i.e. development of specific antitumor reactivity (e.g., tumor-infiltrating lymphocyte therapy) per course of treatment</td>
</tr>
<tr>
<td>ICD-10 Procedure</td>
<td>6A550Z1</td>
<td>Pheresis of Leukocytes, Single</td>
</tr>
<tr>
<td></td>
<td>6A551Z1</td>
<td>Pheresis of Leukocytes, Multiple</td>
</tr>
<tr>
<td></td>
<td>XW033C3</td>
<td>Introduction of Engineered Autologous Chimeric Antigen Receptor T-cell Immunotherapy into Peripheral Vein, Percutaneous Approach, New Technology Group 3</td>
</tr>
<tr>
<td></td>
<td>XW043C3</td>
<td>Introduction of Engineered Autologous Chimeric Antigen Receptor T-cell Immunotherapy into Central Vein, Percutaneous Approach, New Technology Group 3</td>
</tr>
</tbody>
</table>

**Policy History**

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>04/01/2016</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>11/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>12/01/2017</td>
<td>Policy revision with position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>03/01/2018</td>
<td>Coding update</td>
<td>Administrative Review</td>
</tr>
<tr>
<td>05/01/2018</td>
<td>Coding update</td>
<td>Administrative Review</td>
</tr>
</tbody>
</table>

**Definitions of Decision Determinations**

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions,
but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

**Prior Authorization Requirements (as applicable to your plan)**

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.