LOUISIANA BLUE

Adoptive Immunotherapy

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Chimeric Antigen Receptor T cell (CAR-T) therapy is addressed separately in medical policy 00605. Sipuleucel-T (Provenge®) is addressed separately in medical policy 00264. Lifileucel suspension (Amtagvi™) is addressed separately in medical policy 00889. Afamitresgene autoleucel (Tecelra®) is addressed separately in medical policy 00911.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers all adoptive immunotherapy techniques intended to enhance autoimmune effects for the indications including, but not limited to, cancers associated with Epstein-Barr Virus (EBV), Cytomegalovirus (CMV), nasopharyngeal cancer, renal cell carcinoma, gastric cancer, colorectal cancer, hepatocellular carcinoma, non-small cell lung cancer (NSCLC), glioblastoma multiforme, medullary thyroid cancer, pancreatic cancer, and cancers treated with autologous peripheral T lymphocytes containing tumor antigen-specific T cell receptors to be **investigational.***

Note: FDA-approved cellular immunotherapies (e.g., tisagenlecleucel [Kymriah™], axicabtagene ciloleucel [Yescarta™], brexucabtagene autoleucel [Tecartus™], sipuleucel-T [Provenge®], lisocabtagene maraleucel [Breyanzi®], idecabtagene vicleucel [Abecma®], ciltacabtagene autoleucel [Carvykti™], lifileucel suspension [Amtagvi™], afamitresgene autoleucel [Tecelra®])‡ are excluded from this policy and considered separately in their respective medical policies noted above.

Background/Overview

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.

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 lymphodepleting preparative regimen." 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 re-transfused 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.

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

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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

There are currently no adoptive immunotherapy products within the scope of this policy that are U.S. FDA-approved.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

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.

CYTOTOXIC T LYMPHOCYTES

Epstein-Barr Virus–Associated Cancers

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 (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. 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 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 noncomparative 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. 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 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- -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, $p < 0.001$). 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], 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. 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. 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
Two meta-analyses evaluating CIK cell/dendritic cell-cytokine-induced killer (DC-CIK) cell immunotherapy in gastric cancers have been performed and represent a total of 15 studies. Wang et al (2018) evaluated the effect of treatment for gastric cancer after surgery. Compared with the control group, the HR for OS was 0.712 (95% CI, 0.594 to 0.854) and 0.66 (95% CI, 0.546 to 0.797) for overall DFS. No fatal adverse reactions were noted. Fever was the most common adverse event in the CIK/DC-CIK treatment. Other effects (such as nausea and headache) could be relieved without medication or by simple treatment. In addition, CIK/DC-CIK therapy reduced bone marrow suppression caused by chemotherapy. The analysis is limited in several ways. First, the difference between the numbers of patients involved in each study may have led to partial differences in outcomes. Secondly, there were differences in the use of immune cells across different studies. Furthermore, different surgical procedures may have led to different outcomes, thus creating a study bias. Patients in stages I to III underwent radical surgery, whereas patients in stage IV underwent palliative surgery. Du et al (2020) focused their analysis on the combination of CIK/DC-CIK immunotherapy with chemotherapy for the treatment of advanced gastrointestinal cancers, which included both gastric cancers and CRC. Combination therapy was found to be associated with improved OS and PFS compared to chemotherapy alone. Subgroup analyses of the outcomes stratified by gastric cancer and CRC found results were consistent with the overall results. No significant differences in CR, partial response, and overall response rates were noted between the groups. In this analysis, QOL was also assessed using data from 3 of the included trials. Significantly improved QOL was observed in the CIK/DC-CIK immunotherapy group compared with the chemotherapy alone group (n = 245; weighted mean difference = 16.09; 95% CI, 1.66 to 30.52). For safety, no significant differences were noted between groups for adverse events of interest, such as myelosuppression. The analysis was limited by the presence of potential publication bias leading to negative data being omitted.

Subsection Summary: Gastric Cancer
Two meta-analyses have reported statistically significant improvements in OS, DFS, and PFS with the addition of CIK/DC-CIK immunotherapy to chemotherapy compared to 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.

Colorectal Cancer
The systematic review by Du et al (2020) summarized previously for gastric cancer included both gastric cancers and CRC. Their analysis found significant improvements in OS and PFS in favor of the combination of CIK/DC-CIK immunotherapy with chemotherapy compared to chemotherapy alone for the treatment of advanced gastrointestinal cancers. Subgroup analyses of the outcomes stratified by gastric cancer and CRC found results were consistent with the overall results.

A systematic review with meta-analysis by Li et al (2023) evaluated studies comparing CIK to non-CIK therapy in patients with CRC. The analysis included 70 studies, 54 of which were prospective and 15 of which were retrospective, comprising 6743 patients. All studies were conducted at single centers in China. The majority of patients had stage III (17%) or IV disease (46%). Most studies involved CIK/DC-CIK administered alongside FOLFOX (n = 43) or XELOX (n = 24) chemotherapy. In studies with data for OS (n=26 studies involving 3303 patients), the pooled HR for OS with CIK/DC-CIK relative to control was 0.59 (95% CI, 0.53 to 0.65; I^2 = 11%). Pooled OS analysis indicated survival benefit with CIK/DC-CIK relative to control at 1 (relative risk ratio [RR] 0.47; 95% CI, 0.32 to 0.67; I^2 = 51%), 3 (RR 0.67; 95% CI, 0.59 to 0.77; I^2 = 32%), and 5 years (RR 0.69; 95% CI, 0.54 to 0.88; I^2 = 73%). Similarly, in studies with data for PFS (n = 20 studies involving 2593 patients), the pooled HR for PFS with CIK/DC-CIK relative to control was 0.55 (95% CI, 0.47 to 0.63) with moderate heterogeneity (I^2 = 54%; p = 0.002). Pooled PFS analysis indicated survival benefit with CIK/DC-CIK relative to control at 1 (RR 0.43; 95% CI, 0.33 to 0.55; I^2 = 0%), 3 (RR 0.76; 95% CI, 0.66 to 0.87; I^2 = 53%), and 5 years (RR 0.71; 95% CI, 0.59 to 0.87; I^2 = 68%). Most studies reported toxicity in a descriptive manner. Sensitivity analyses indicated similar results to the overall analysis for OS for subgroups of randomized (HR 0.57; 95% CI, 0.50 to 0.66) or non-randomized studies (HR 0.59; 95% CI, 0.51 to 0.67), studies involving patients with stage IV (HR 0.57; 95% CI, 0.50 to 0.65) or earlier-stage CRC (HR 0.64; 95% CI, 0.48 to 0.85), and studies of CIK (HR 0.57; 95% CI, 0.47 to 0.69) or DC-CIK (HR 0.61; 95% CI, 0.54 to 0.69).

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). 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. A meta-analysis that included both gastric cancer and CRC and another meta-analysis of studies of CRC found improvements in OS and PFS in favor of CIK/DC-CIK compared to 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
Two meta-analyses have evaluated the efficacy of CIK, DC, or DC-CIK immunotherapy combined with conventional treatments in HCC. Cao et al (2019) evaluated CIK, DC, or DC-CIK immunotherapy in 22 trials. Cai et al (2017) reported on outcomes of conventional treatments plus sequential CIKs compared to conventional treatments alone. For both studies, all studies evaluating CIK or DC-CIK immunotherapy were conducted in Asia and were limited by the variety of comparators included, some of which do not reflect current practice.

Subsection Summary: Hepatocellular Carcinoma
Several RCTs and quasi-RCTs have evaluated the efficacy of CIK cells in hepatocellular cancers. Meta-analysis of these trials have reported improved OS rates when compared to conventional therapies alone. Included studies in meta-analyses 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, heterogenous treatment groups, and other methodological 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 DC 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
EBV-associated Nasopharyngeal Carcinoma
Liang et al (2023) performed an open-label phase 2 RCT of adjuvant TIL infusion 1 week after completion of chemoradiation in patients with advanced EBV-associated nasopharyngeal carcinoma who had pre-treatment EBV DNA levels $\geq$ 4,000 copies/mL. The primary outcome was investigator-assessed PFS. Median follow-up was 62.3 months. Compared with patients randomized to receive chemoradiation alone (n = 78), 3-year PFS in patients randomized to adjuvant TIL therapy (n = 78) was not significantly different (74.4% vs 75.6%; HR 1.08, 95% CI, 0.62 to 1.89). No significant

differences were identified between groups in OS or cumulative incidence of locoregional or distant metastatic relapse.

Subsection Summary: Epstein-Barr Virus-Associated Nasopharyngeal Carcinoma
An RCT of TILs used as adjuvant therapy to chemoradiation in patients with EBV-associated nasopharyngeal carcinoma demonstrated similar PFS and other outcomes relative to chemoradiation alone. Larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as a control arm showing treatment benefits are needed.

DENDRITIC CELLS
Antigen-loaded autologous dendritic cells (ADCs) have been explored primarily in early-stage trials in various malignancies including lymphoma, myeloma, subcutaneous tumors, melanoma, NSCLC, renal cell cancer, and cervical cancer. A 2012 systematic review highlighted progress in DC-based immunotherapy in epithelial ovarian cancer.

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. 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%).

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 DC/CIK combination immunotherapy as maintenance treatment of advanced NSCLC. 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/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 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. 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; I^2 = 35%; RR for 2-year OS = 2.88; 95% CI, 1.38 to 5.99; p = 0.005; I^2 = 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/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. 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 DC-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.

TCR Therapy

Yarza et al (2023) performed a systematic review with patient-level network meta-analysis of randomized and non-randomized studies evaluating TCRs for patients with cutaneous melanoma, with the aim of estimating the effect of this intervention. The analysis included data for 187 patients from 14 studies. Pooled objective response rate (ORR) was 28% (95% CI, 20 to 37; I^2 = 86.9%) and disease control rate was 38% (95% CI, 27 to 50; I^2 = 93.1%). Median PFS was 2.9 months (95% CI, 1.4 to 3.1). Median duration of response was 6.8 months (95% CI, 4.1 to 11.1) for patients who achieved partial response and was not reached (95% CI, 24.1 to not reached) for patients who achieved complete response. Toxicity was not analyzed.

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 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 (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. A patient-level network meta-analysis involving data for 187 patients with cutaneous melanoma who received TCR therapy indicated an ORR of 28% with median PFS of 2.9 months in patients who achieved partial response; median PFS was not reached in patients who achieved complete response. This evidence does not demonstrate net health benefit with genetically engineered T cells in patients with metastatic melanoma.

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 2 meta-analyses encompassing non-randomized trials. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. Both meta-analyses reported statistically significant effects on OS, DFS, and PFS in favor of immunotherapy versus 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 that the technology results in an improvement in the net health outcome.

For individuals with colorectal cancer (CRC) who receive CIK cells, the evidence includes a single RCT and 2 meta-analyses. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. Results of the RCT showed a statistically significant effect on OS in favor of immunotherapy versus chemotherapy alone. A meta-analysis that included both gastric cancer and CRC found improvements in OS and PFS in favor of CIK or CIK cell/dendritic cell-cytokine-induced killer (DC-CIK) cells compared to chemotherapy alone; another meta-analysis of prospective and randomized studies of CIK or DC-CIK in patients with CRC also showed improvements in survival outcomes compared to non-CIK/DC-CIK treatments. 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 that the technology results in an improvement in the net health outcome.

For individuals with hepatocellular carcinoma (HCC) who receive CIK cells, the evidence includes meta-analyses that include RCTs and quasi-randomized trials. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. Meta-analyses of these trials have reported improved OS rates when compared to conventional therapies alone, but they are limited by inclusion of studies from Asia only and heterogeneity in comparators. This body of evidence is limited by the context of the studies (non-U.S.), small sample sizes, heterogeneous treatment groups, and other methodological 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 that the technology results in an improvement in the net health outcome.

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.

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 T Lymphocytes

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

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Policy History

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02/04/2010	Medical Policy Committee review.
02/17/2010	Medical Policy Implementation Committee approval
02/03/2011	Medical Policy Committee review.
02/16/2011	Medical Policy Implementation Committee approval. No changes to coverage.
02/02/2012	Medical Policy Committee review.
02/15/2012	Medical Policy Implementation Committee approval. No changes to coverage.
02/07/2013	Medical Policy Committee review.
02/20/2013	Medical Policy Implementation Committee approval. Coverage statement reworded to include cytokine-induced killer (CIK) cells to the list of investigational indications.
02/06/2014	Medical Policy Committee review.
02/19/2014	Medical Policy Implementation Committee approval. No change to coverage.
02/05/2015	Medical Policy Committee review.
02/18/2015	Medical Policy Implementation Committee approval. No change to coverage.
02/04/2016	Medical Policy Committee review.
02/17/2016	Medical Policy Implementation Committee approval. Section on lymphokine-activated killer cell deleted due obsolete intervention.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
02/02/2017	Medical Policy Committee review.
02/15/2017	Medical Policy Implementation Committee approval. No change to coverage.
02/01/2018	Medical Policy Committee review.
02/21/2018	Medical Policy Implementation Committee approval. Policy background and rationale updated to include most current evidence.

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02/07/2019	Medical Policy Committee review.
02/20/2019	Medical Policy Implementation Committee approval. No change to coverage.
02/06/2020	Medical Policy Committee review.
02/12/2020	Medical Policy Implementation Committee approval. No change to coverage.
02/04/2021	Medical Policy Committee review
02/10/2021	Medical Policy Implementation Committee approval. Policy background and references updated. Investigational statement updated for clarity. No change to coverage.
02/03/2022	Medical Policy Committee review
02/09/2022	Medical Policy Implementation Committee approval. No change to coverage.
02/02/2023	Medical Policy Committee review
02/08/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/01/2024	Medical Policy Committee approval
02/14/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/06/2025	Medical Policy Committee review
02/12/2025	Medical Policy Implementation Committee approval. Policy background and references updated. Investigational statement updated for clarity. No change to coverage.

Next Scheduled Review Date: 02/2026

Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0708T, 0709T, 38999
HCPCS	M0075, S2107
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: 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 eligibility for coverage.