Adoptive Immunotherapy

Policy # 00248
Original Effective Date: 02/17/2010
Current Effective Date: 02/21/2018

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.

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 applications of adoptive immunotherapy other than FDA-approved Chimeric Antigen Receptor T cell (CAR-T) therapies to be **investigational.***

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

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.

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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 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.

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)
Adoptive immunotherapy is not a U.S. FDA–regulated procedure.

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Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Adoptive immunotherapy has been investigated for the treatment of relatively common cancers in which novel treatments have been adopted when 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.

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-α-2a (arm 2, n=74). The primary end point was OS, and the secondary end point was PFS evaluated by Kaplan-Meier analyses and hazard ratios (HRs) with Cox proportional hazards models. Three-year PFS and OS rates in arm 1 were 18% and 61%, respectively, vs 12% and 23%, respectively, in arm 2 (p=0.031 and p<0.001, respectively). Median PFS and OS in arm 1 were significantly longer than those in arm 2 (PFS, 12 months vs 8 months, p=0.024; OS, 46 months vs 19 months, p<0.001). 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
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. 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 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. 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). 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, I^2=48).

Yu et al (2014) conducted an RCT in China of 132 patients who had previously untreated hepatocellular carcinoma. 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).

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. 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 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
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, 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.

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. One patient had a partial response, two had stable disease for more than 6 months, and two had disease progression. Toxicities included grade 1 anemia and grade 2 leukocytopenia, nausea, and constipation.

Subsection Summary: Pancreatic Cancer
A small prospective noncomparative study in 5 patients with pancreatic cancer treated with ADCs and lymphokine-activated killer has been published. There are no RCTs comparing DC-based adoptive immunotherapy with 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
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. 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 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. 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.

Adoptive Immunotherapy

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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

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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.

Next Scheduled Review Date: 02/2019

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Code Type	
CPT	37799, 38999
HCPCS	S2107
ICD-10 Diagnosis	All related diagnoses

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A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. 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 the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);

2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
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