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Adoptive Immunotherapy

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Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

All adoptive immunotherapy techniques intended to enhance autoimmune effects **are considered experimental, investigational and/or unproven** for the indications included, but not limited to, cancers associated with Epstein-Barr virus, *Cytomegalovirus*-associated cancers, nasopharyngeal cancer, renal cell carcinoma, gastric cancer, colorectal cancer, hepatocellular carcinoma, non-small-cell lung cancer, melanoma, glioblastoma multiforme, medullary thyroid cancer, pancreatic cancer, and cancers treated with autologous peripheral T lymphocytes containing tumor antigen-specific T cell receptors.

Policy Guidelines

NOTE 1: Allogeneic cell transplantation following nonmyeloablative conditioning of the recipient (known as reduced-intensity conditioning or RIC) may also be referred to as "adoptive immunotherapy" in the literature. However, RIC cell transplantation relies on a donor-versus-malignancy effect of donor lymphocytes. In contrast, the adoptive immunotherapy techniques described in this policy enhance autoimmune effects primarily. The use of RIC in cell transplantation is discussed for specific cancers in individual policies related to cell transplantation.

NOTE 2: See RX502.061 "Oncology Medications" for information on genetically engineered T-cell therapy (e.g., axicabtagene ciloleucel, tisagenlecleucel, brexucabtagene autoleucel).

Description

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

Background

Health Disparities in Certain Cancers

Hepatic tumors can arise as primary liver cancer (hepatocellular cancer) or by metastasis to the liver from other tissues. A study from 2016 determined that the incidence of liver cancer was higher among White individuals, Black individuals, and Hispanic individuals born after 1938. (1) The incidence of hepatocellular carcinoma was twice as high for U.S.-born Hispanic men compared to Hispanic men born outside of the US. This may be due to the increased risk of smoking, hepatitis B or C infection, and diabetes among U.S.-born Hispanic individuals.

Based on data from 2016 through 2021, kidney cancer is more common in men than women and occurs more often in non-Hispanic American Indian, Alaskan Native individuals, and non-Hispanic Black individuals compared to individuals of other races or ethnicities. (2) American Indians and Alaska Natives have higher death rates from kidney cancer than any other racial or ethnic group. A cohort study by Howard et al. (2021) included 158,445 patients with localized kidney cancer from the National Cancer Database between 2010 and 2017. (3) Investigators found that that female patients were treated more aggressively compared with male patients, with lower adjusted odds of undertreatment and higher adjusted odds of overtreatment. They also found that Black and Hispanic patients had higher adjusted odds of undertreatment and overtreatment compared to White patients, and uninsured status was associated with lower adjusted odds of overtreatment and higher adjusted odds of undertreatment. These results

suggest that sex, race and ethnicity, and socioeconomic status are associated with disparities in guideline-based treatment for localized kidney cancer, specifically, with increased rates of non-guideline based treatment for women and Black and Hispanic patients.

Adoptive Immunotherapy

Adoptive immunotherapy uses "activated" lymphocytes or other immune cells as a treatment modality. (4) Both nonspecific and specific lymphocyte activation are used therapeutically. The nonspecific, polyclonal proliferation of lymphocytes by cytokines (immune system growth factors), also called autolymphocyte therapy, increases the number of activated lymphocytes.

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 (IL)-2 and other cytokines. More recent techniques have yielded select populations of CTL with specific reactivity to tumor antigens. Peripheral lymphocytes are propagated in vitro with antigen-presenting dendritic cells (DC) that have been pulsed with tumor antigens. Alternatively, innate tumor-infiltrating lymphocytes (TIL) from the tumor biopsy are propagated in vitro with IL-2 and anti-CD3 antibody, a T-cell activator. The 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 (CIK) 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. (5)

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 DC infusions.

Adoptive cellular therapy is "the administration of a patient's own (autologous) or donor (allogeneic) antitumor lymphocytes following a lymphodepleting preparative regimen." (6) Protocols vary, but include these common steps:

- Lymphocyte harvesting (either from peripheral blood or from tumor biopsy)
- Propagation of tumor-specific lymphocytes in vitro using various immune modulators
- Selection of lymphocytes with reactivity to tumor antigens with enzyme-linked immunosorbent assay
- Lymphodepletion of the host with immunosuppressive agents
- Adoptive transfer (i.e., transfusion) of lymphocytes back into the tumor-bearing host.

Dendritic cell-based immunotherapy uses autologous DC (ADC) to activate a lymphocyte-mediated cytotoxic response against specific antigens in vivo. Autologous dendritic cells 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 have used various cytokines (e.g., IL-7 and IL-15 instead of IL-2) to propagate lymphocytes. Protocols also differ in the extent of host lymphodepletion induced prior to transfusing lymphocytes to the tumor-bearing host.

Regulatory Status
There are currently no adoptive immunotherapy products within the scope of this policy that are U.S. Food and Drug Administration (FDA)-approved.

Rationale

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 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. Randomized controlled trials 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 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 (RCC) (7) and postoperative hepatocellular carcinoma (HCC). (8, 9)

Cytotoxic T Lymphocytes

Clinical Context and Therapy Purpose

The purpose of cytotoxic T lymphocytes (CTL) is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with Epstein-Barr virus (EBV)-associated cancers or with *Cytomegalovirus*-associated cancers.

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

Populations

The relevant population of interest is individuals with EBV-associated or *Cytomegalovirus*-associated cancers.

Interventions

The therapy being considered is CTL.

Comparators

Comparators of interest include standard of care.

Outcomes

The general outcomes of interest are overall survival (OS), disease-specific survival (DSS), QOL, treatment-related mortality, and treatment-related morbidity.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.
- The version of the therapeutic is described.
- Patient/sample clinical characteristics are described.
- Patient/sample selection criteria are described.

Epstein-Barr Virus–Associated Cancers

Yeo et al. (2024) conducted a meta-analysis of 6 studies that evaluated EBV-specific CTL monotherapy in EBV-positive recurrent or metastatic nasopharyngeal carcinoma. (10) The authors reported a pooled progressive disease rate of 54% (95% CI, 9% to 93%; I^2=56%), a stable disease rate of 22% (95% CI, 2% to 75%; I^2=5%), and the pooled incidence of any-grade adverse events with CTL therapy of 45%. Across the CTL monotherapy studies that reported safety (80 patients), there were 136 non-hematologic adverse events, with 4 high-grade events (grade-3 bleeding; grade-5 pulmonary insufficiency; grade-5 sepsis; grade-3 lung abscess); the

remaining adverse events were predominantly grade 1 or 2 vaccine-like reactions (e.g., fever/fatigue). Four deaths were described across 3 CTL studies.

Randomized Controlled Trials

Toh et al. (2024) conducted a multicenter, randomized phase III study across 30 sites in Asia and the United States, enrolling 330 patients with recurrent or metastatic EBV-positive nasopharyngeal carcinoma. (11) Participants received either first-line gemcitabine/carboplatin (GC) chemotherapy alone or GC followed by sequential infusions of autologous EBV-specific CTLs. The trial did not achieve its primary endpoint, demonstrating no statistically significant improvement in median OS between treatment arms (25.0 months for GC + CTL vs. 24.9 months for GC alone; Hazard Ratio [HR], 1.19; 95% CI, 0.91 to 1.56; p=.194). Similarly, median progression-free survival showed no benefit for the combination therapy (7.9 months vs. 8.6 months; HR, 1.34; 95% CI, 1.04 to 1.73). Both treatment groups had comparable objective response rates. The CTL therapy demonstrated minimal treatment-related toxicity, including only 1 grade ≥ 3 adverse event (anemia) and 1 grade 2 serious adverse event (pyrexia) attributable to CTL therapy.

Observational Studies

Bollard et al. (2014) conducted an international prospective cohort study of CTL therapy in patients with EBV–positive Hodgkin or non-Hodgkin lymphoma. (12) Patients had either active, relapsed disease (n=21) or were in remission with a high-risk of relapse (n=29). CTL 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. (13) Patients received standard chemotherapy with gemcitabine and carboplatin followed by EBV-specific CTL infusion. Median progression-free survival (PFS) and OS were 8 months and 30 months, respectively. One-, 2-, and 3-year OS rates were 77%, 63%, and 37%, respectively. In comparison, median OS in a group of similar historical controls treated at the same institution with chemotherapy only was 18 to 21 months, and 2- and 3-year OS rates were 30% to 43% and 16% to 25%, respectively. The most common adverse events associated with CTL infusion were grade 1 and 2 fatigue and grade 1 myalgia. Two patients developed transient fever, and 3 patients developed grade 1 skin rash. Grade 3 or higher hematologic or nonhematologic toxicities were not observed during CTL therapy. In a Japanese series of 7 patients who received CTLs for advanced oral and maxillofacial cancers, Ohtani et al. (2014) reported 1-year survival rates in patients who achieved response (n=3) and in those with progressive disease (n=4) of 100% and 25%, respectively, although definitions of response were unclear. (14)

Subsection Summary: Epstein-Barr Virus–Associated Cancers

A RCT and 2 small, prospective noncomparative cohort studies in patients with relapsed disease have indicated a response to infused CTLs directed against cancer-associated viral antigens. Adverse events were mild or moderate. A phase III randomized controlled trial found no significant difference in overall or progression-free survival between patients with EBV-positive nasopharyngeal carcinoma treated with chemotherapy alone versus chemotherapy followed by CTL therapy. To establish efficacy, the following are needed: large, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit.

Cytomegalovirus-Associated Cancers

Observational Studies

Schuessler et al. (2014) administered CTLs with or without chemotherapy to 13 patients with recurrent glioblastoma multiforme. (15) CTL 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 CTLs has reported mild adverse events. There are no RCTs comparing CTL with the standard of care and therefore no conclusions can be made about the efficacy of CTL in *Cytomegalovirus*-associated cancers. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit.

Cytokine-Induced Killer Cells

Clinical Context and Therapy Purpose

The purpose of cytokine-induced killer (CIK) cells is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with various malignancies.

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

Populations

The relevant population of interest is individuals with various malignancies, including nasopharyngeal carcinoma, RCC, gastric cancer, colorectal cancer (CRC), HCC, and non-small-cell lung cancer (NSCLC).

Interventions

The therapy being considered is CIK cells.

Comparators

Comparators of interest include standard of care.

Outcomes

The general outcomes of interest are OS, DSS, QOL, treatment-related mortality, and treatment-related morbidity.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.
- The version of the therapeutic is described.
- Patient/sample clinical characteristics are described.
- Patient/sample selection criteria are described.

Nasopharyngeal Carcinoma

Randomized Controlled Trials

Li et al. (2012) conducted an RCT to evaluate the efficacy of autologous CIK transfusion in combination with gemcitabine and cisplatin (GC) chemotherapy to treat nasopharyngeal carcinoma in patients with distant metastasis after radiotherapy. (16) 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 versus 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=.137). Median PFS was 26 months for the GC plus CIK group and 19 months for the GC group (p=.023). This small, single-center RCT suggests that the combination of CIK cells and GC regimen chemotherapy may be a viable treatment option for patients with advanced nasopharyngeal carcinoma.

Subsection Summary: Nasopharyngeal Carcinoma

A single RCT from China reported a 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 methodological weaknesses (inadequate reporting of randomization, allocation concealment, and power). To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit.

Renal Cell Carcinoma

Randomized Controlled Trials

Liu et al. (2012) conducted an RCT to evaluate the effects of autologous CIK cell immunotherapy in patients with metastatic RCC followed in another university cancer center in China. (17) From 2005 to 2008, 148 patients were randomized to autologous CIK cell immunotherapy (arm 1, n=74) or interleukin-2 (IL-2) treatment in combination with human interferon-α-2a (arm 2, n=74). The primary endpoint was OS, and the secondary endpoint 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, versus 12% and 23%, respectively, in arm 2 (p=.031 and p<.001, respectively). Median PFS and OS in arm 1 were significantly longer than those in arm 2 (PFS, 12 months vs. 8 months, p=.024; OS, 46 months vs. 19 months, p<.001), respectively. Multivariate analyses indicated that the cycle count of CIK cell immunotherapy as a continuous variable was significantly associated with prolonged PFS (HR=0.88; 95% confidence interval [CI], 0.84 to 0.93; p<.001) and OS (HR 0.58; 95% CI, 0.48 to 0.69; p<.001) in arm 1. These findings suggest that CIK cell immunotherapy has the potential to improve the prognosis of patients with metastatic RCC.

Zhang et al. (2013) conducted a small RCT in China that assessed 20 patients who had unilateral, locally advanced RCC after nephrectomy. (18) Patients were randomized 1:1 to postoperative CIK therapy or usual care (chemotherapy with or without radiotherapy, additional surgery, or no further treatment). Method of randomization was not described. At a median follow-up of 44 months, 6 patients in the CIK group and 5 controls achieved CR; 2 patients in the CIK group and no controls achieved partial response (overall objective response, 80% in the CIK group vs. 50% in the control group; p=.175). Mean PFS was significantly longer in the CIK group, but OS was not (mean PFS, 32 months vs. 22 months; p=.032; mean OS, 35 months vs. 34 months; p=.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 RCC. (19) Dendritic cells were also incorporated into treatment. Among the 60 operable patients, the 3-year disease-free survival (DFS) rate was 96.7% compared with 57.7% in the control group. PFS was also longer in the CIK group (p=.021). Among the 62 inoperable patients, OS was longer in the CIK group (p=.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 RCC. The largest of the 3 RCTs reported statistically significant gains in PFS and OS with CIK cell immunotherapy compared with 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 other 2 RCTs also reported response rates in favor of CIK therapy with inconsistent effects on survival. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit.

Gastric Cancer

Systematic Reviews

Two meta-analyses evaluating CIK cell/dendritic cell-cytokine-induced killer (DC-CIK) cell immunotherapy in gastric cancers are summarized in Tables 1 to 3. Wang et al. (2018) evaluated the effect of treatment for gastric cancer after surgery. (20) 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 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. (21) 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.

Table 1. Comparison of Studies Included in Gastric Cancer Meta-analyses

Study	Du et al. (2020) (21)	Wang et al. (2018) (20)
Jiang (2006)	●	
Shi (2012)	●	●
Zhao (2013)	●	
Lin (2015)	●	
Mu (2016)	●	
Zhao (2016)	●	
Peng (2017)	●	
Wang (2017)	●	●
Xie (2017)	●	
Liu (2013)		●
Yu (2015)		●
Zhao (2012)		●
Li (2017)		●
Gao (2013)		●

Cu (2015)		●

Table 2. Gastric Cancer Meta-Analyses Characteristics

Study	Dates	Trials	Participants	Comparison	N(Range)	Design	Duration
Du et al. (2020) (21)	2006-2017	9	Patients with advances gastrointestinal cancer (gastric cancer or CRC)	CIK/DC-CIK immunotherapy combined with chemotherapy versus chemotherapy alone	1113 (28 to 255)	3 prospective and 6 retrospective studies	At least 24 months
Wang et al. (2018) (20)	2010-2017	9	Patients with gastric cancer post-surgery	CIK/DC-CIK immunotherapy combined with chemotherapy versus chemotherapy alone	1213 (54 to 226)	7 quasi-RCTs and 2 controlled trials	NR

CIK: cytokine-induced killer cell; CRC: colorectal cancer; DC: dendritic cell; NR: not reported; RCT: randomized-controlled trials.

Table 3. Gastric Cancer Meta-Analyses Results

Study	OS		DFS		PFS	
	3-year	**5-year**	**3-year**	**5-year**	**3-year**	**5-year**
Du et al. (2020) (21)						
Total N	727	580			727	580
Pooled effect (95% CI)	1.43 (1.25 to 1.64)	1.84 (1.41 to 2.40)			1.39 (1.20 to 1.62)	1.99 (1.52 to 2.60)
I^2 (p)	36.3% (0.179)	0% (0.654)			0% (0.664)	0% (0.727)
Wang et al. (2018) (20)						
Total N	627	526	529	370		
Pooled effect (95% CI)	1.29 (1.15 to 1.48)	1.73 (1.36 to 2.19)	1.40 (1.19 to 1.65)	2.10 (1.53 to 2.87)		
I^2 (p)	0% (0.89)	0% (0.62)	9% (0.35)	0% (0.57)		

CI: confidence interval; DFS: disease-free survival; OS: overall survival; PFS: progression-free survival.

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

Systematic Reviews

The systematic review by Du et al. (2020) summarized previously for gastric cancer included both gastric cancers and CRC. (21) 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. (22) 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=.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).

Randomized Controlled Trials

Zhao et al. (2016) reported the results of a controlled trial in which 122 patients with metastatic CRC were randomized to CIK cell immunotherapy plus chemotherapy (n=61) or chemotherapy alone (n=61). (23) The primary study endpoint was OS. The median OS was significantly greater with CIK cell immunotherapy plus chemotherapy (36 months) than with chemotherapy alone (16 months; p<.001). The 3-year OS rates for both groups were 48% and 23%, respectively (p<.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 versus 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 are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit.

Hepatocellular Carcinoma

Systematic Reviews

Two meta-analyses have evaluated the efficacy of CIK, DC, or DC-CIK immunotherapy combined with conventional treatments in HCC, which are summarized in Tables 4 to 6. Cao et al. (2019) evaluated CIK, DC, or DC-CIK immunotherapy in 22 trials. (24) Cai et al. (2017) reported on outcomes of conventional treatments plus sequential CIKs compared to conventional treatments alone. (25) 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.

Table 4. Comparison of Studies Included in Hepatocellular Carcinoma Meta-analyses

Study	Cao et al. (2019) (24)	Cai et al. (2017) (25)
Weng (2007)	●	●
Dong (2008)	●	
Hao (2010)	●	●
Pan (2010)	●	
Pan (2013)	●	
Lee (2015)	●	●
Pan (2015)	●	
Chen (2016)	●	
Li (2016)	●	
Chang (2018)	●	
Lee (2018)	●	
Cui (2014)	●	●
Qian (2016)	●	
Qui (2011)	●	●
Niu (2013)	●	
Takamaya (2000)		●
Hui (2009)		●
Wang (2012)		●
Xu (2013)		●
Yu (2014)		●

Zhang (2014)		●
Xu (2016)		●

5 studies included in the Cao et al. (2019) analysis evaluated DC-monotherapy with conventional treatments; these studies are not included in the table summary.

Table 5. Hepatocellular Carcinoma Meta-Analyses Characteristics

Study	Dates	Trials	Participants	Comparison	N(Range)	Design	Duration
Cao et al. (2019) (24)	2007-2018	22	Patients with HCC receiving CIK, DC-CIK, or DC immunotherapy	CIK/DC–CIK/DC immunotherapy combined with conventional therapy vs conventional therapy alone	3756 (18 to 1031)	7 RCTs, 15 non-randomized controlled trials	NR
Cai et al. (2017) (25)	2000-2016	12	Patients with HCC receiving sequential CIKs with conventional treatments	CIK immunotherapy combined with conventional therapy vs conventional therapy alone	1387 (18 to 226)	9 RCTs and 3 quasi-RCTs	NR

CIK: cytokine-induced killer cell; DC: dendritic cell; HCC: hepatocellular carcinoma; NR: not reported; RCT: randomized controlled trials.

Table 6. Hepatocellular Carcinoma Meta-Analyses Results

Study	OS		PFS
Cao et al. (2019) (24)	3-year	5-year	
Total N	2582	2306	
Pooled effect (95% CI)	1.23 (1.15-1.31)	1.26 (1.15 to 1.37)	
I^2 (p)	0% (0.77)	0% (0.88%)	
Cai et al. (2017) (25)	Overall HR (duration not specified)		Overall HR (duration not specified)
Total N	NR		NR
Pooled effect (95% CI)	0.59 (0.46 to 0.77)		0.53 (0.40 to 0.69)
I^2 (p)	48% (0.03)		0% (0.85)

CI: confidence interval; HR: hazard ratio; NR, not reported; OS: overall survival; PFS: progression-free survival.

Subsection Summary: Hepatocellular Carcinoma

Several RCTs and quasi-RCTs have evaluated the efficacy of CIK cells in HCC. 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, 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.

Non-Small-Cell Lung Cancer

Systematic Reviews

Zhong et al. (2024) conducted a meta-analysis of RCTs evaluating autologous CIK cells combined with chemotherapy for NSCLC. (26) Eleven RCTs (N=924) published between 2015 and 2021 were included; all were conducted in China, and sample sizes were modest, with the largest trial enrolling 61 CIK-treated and 61 control patients. The pooled analysis demonstrated that CIK combined with chemotherapy significantly improved treatment efficacy (Odds Ratio [OR], 1.91; p=.02) and disease control rate (OR, 3.34; p<.001) compared to chemotherapy alone. Additionally, the combination therapy significantly reduced adverse effects such as bone marrow suppression, liver injury, and gastrointestinal symptoms compared to chemotherapy alone (p<.05).

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 treatment efficacy and disease control rate. The included body of evidence in the systematic review 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.

Tumor-Infiltrating Lymphocytes

Clinical Context and Therapy

The purpose of tumor-infliltrating lymphocytes (TIL) is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with cancers including EBV-associated nasopharyngeal carcinoma.

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

Populations

The relevant population of interest is individuals with cancers including melanoma and EBV-associated nasopharyngeal carcinoma.

Interventions

The therapy being considered is TIL.

Comparators

Comparators of interest include standard of care.

Outcomes
The general outcomes of interest are OS, DSS, QOL, treatment-related mortality, and treatment-related morbidity.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.
- The version of the therapeutic is described.
- Patient/sample clinical characteristics are described.
- Patient/sample selection criteria are described.

Randomized Controlled Trials
Randomized controlled trials of TIL therapy are summarized in Tables 7 to 10. 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 ≥4000 copies/mL. (27) 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.

Table 7. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
Liang et al. (2023) (27)	China	1	2015-2018	N=156 with EBV-associated NPC	ChemoRT plus adjuvant autologous TILs (n=78)	ChemoRT alone (n=78)

ChemoRT: concomitant chemoradiation therapy; EBV: Epstein-Barr virus; NPC: nasopharyngeal carcinoma; RCT: randomized controlled trial; TIL: tumor-infiltrating lymphocyte.

Table 8. Summary of Key RCT Results

Study	PFA (95% CI)	OS (95% CI)
Liang et al. (2023) (27)		
ChemoRT plus autologous TILs	3 y: 75.6% (64.5 to 83.7)	NR

ChemoRT alone	3 y: 74.4% (63.1 to 82.6)	NR
Difference (95% CI)	HR 1.08 (0.62 to 1.89)	HR 1.15 (0.57 to 2.29)

ChemoRT: concomitant chemoradiation therapy; CI: confidence interval; HR: hazard ratio; NR: not reported; OS: overall survival; PFS: progression-free survival; RCT: randomized controlled trial; TIL: tumor-infiltrating lymphocyte; y: year.

Table 9. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Liang et al. (2023) (27)					

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

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 10. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Liang et al. (2023) (27)		1, 2, 3.				

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

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.

[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.

[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.

[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.

[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to

event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

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, (28) myeloma, (29, 30) subcutaneous tumors, (31) glioma, (32) melanoma, (33) NSCLC, (34, 35), RCC, (36) and cervical cancer. (37) A systematic review by Tanyi and Chu (2012) highlighted progress in DC-based immunotherapy in epithelial ovarian cancer. (38) A meta-analysis of 13 RCTs involving 1,443 patients (730 receiving DC-CIK immunotherapy and 713 controls) across various solid tumors (lung, gastric, liver, colorectal cancers) found that the combined dendritic cell cytokine-induced killer cell therapy significantly improved OS, PFS, overall response rate, and disease control rate compared to control treatments. (39)

Clinical Context and Therapy Purpose
The purpose of DC is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with various malignancies.

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

Populations
The relevant population of interest is individuals with various malignancies, including glioblastoma multiforme, NSCLC, medullary thyroid cancer (MTC), and pancreatic cancer.

Interventions
The therapy being considered is DC.

Comparators
Comparators of interest include standard of care.

Outcomes
The general outcomes of interest are OS, DSS, QOL, treatment-related mortality, and treatment-related morbidity.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.
- The version of the therapeutic is described.
- Patient/sample clinical characteristics are described.
- Patient/sample selection criteria are described.

Glioblastoma Multiforme

Systematic Reviews

Wong et al. (2024) conducted a meta-analysis examining phase II and III trials of autologous dendritic cell (ADC) vaccination combined with standard of care (SOC) versus SOC alone in glioblastoma patients. (40) The analysis incorporated 7 trials totaling 3,619 patients (470 receiving ADC+SOC and 3,149 receiving SOC alone). DC vaccination demonstrated significant survival benefits, with improved OS (HR, 0.71; 95% CI, 0.57 to 0.88) and progression-free survival (Hazard Ratio [HR], 0.65; 95% CI, 0.43 to 0.98). In the newly diagnosed patient subgroup, OS showed marginal improvement (HR, 0.80; 95% CI 0.64 to 1.00) while PFS was improved (HR, 0.59; 95% CI 0.39 to 0.90). Although all studies used ADCs, the methodology for generating and administering the vaccines was not standardized; the studies also exhibited moderate heterogeneity on pooled analysis for overall survival (I^2=47%) and substantial heterogeneity for progression-free survival (I^2=89%).

Randomized Controlled Trials

Liau et al. (2022) reported a phase III, prospective, externally controlled trial of autologous tumor-lysate–loaded dendritic cell vaccination (DCVax-L) added to SOC for newly diagnosed (nGBM) and recurrent GBM (rGBM) across 94 sites (N=331; randomized 2:1, with crossover to DCVax-L at first recurrence). (41) In nGBM, median OS was 19.3 months from randomization with DCVax-L versus 16.5 months in matched contemporaneous external controls (HR, 0.80; p=.002; 98% CI, 0.00 to 0.94). In rGBM (placebo patients who crossed over at recurrence), median OS was 13.2 vs 7.8 months (HR, 0.58; p<.001; 98% CI, 0.00 to 0.76), with higher 24- and 30-month survival landmarks (20.7% vs. 9.6% and 11.1% vs 5.1%). Progression-free survival was not significantly different (6.2 vs. 7.6 months; p =.47), which the authors attribute to adjudication challenges and pseudoprogression. Safety was favorable across 2,151 doses: 5 serious adverse events were possibly related (intracranial edema n=3 [2 grade 3], nausea n=1 [grade 3], lymph-node infection n=1 [grade 3]); no autoimmune reactions or cytokine storm were observed. Limitations included the absence of reported power calculations, the use of external controls for measuring overall survival data, and an open-label design after individuals in the control arm crossed over following recurrence.

Subsection Summary: Glioblastoma Multiforme

A systematic review and meta-analysis of phase II and III trials, using open-label designs or external controls, evaluated ADC vaccination for glioblastoma and found significant improvements in overall and progression-free survival across both newly diagnosed and recurrent populations, although with substantial heterogeneity and non-standardized vaccine manufacturing and administration. A Phase III externally controlled study of DC vaccination plus standard of care also reported longer overall survival in both newly diagnosed and recurrent disease, without a progression-free survival advantage. Given the reliance on non-propensity-matched external controls for overall survival estimates, causal inference remains limited. However, safety appeared acceptable, and the data suggest a potential overall-survival benefit that should be confirmed in an additional trial with appropriate controls.

Non-Small-Cell Lung Cancer

Systematic Reviews

Chen et al. (2014) in China conducted a systematic review and meta-analysis of RCTs that compared combination DC plus CIK immunotherapy with any other treatment (placebo, no intervention, conventional treatment, or other complementary and alternative medicines) for any cancer type and stage. (42) Two RCTs compared DC plus CIK and chemotherapy with chemotherapy alone in patients with stage III or IV NSCLC and reported OS estimates (N=150). Pooled relative risk favored DC plus CIK therapy at 2 years but not at 1 year (relative risk for 1-year OS 1.38; 95% CI, 1.00 to 1.90; p=.05; I^2=35%; relative risk for 2-year OS 2.88; 95% CI, 1.38 to 5.99; p=.005; I^2=0%).

The systematic review by Wang et al. (2014) (discussed previously) also included many studies that used DC in combination with CIK. (43)

Randomized Controlled Trials

Shi et al. (2012) conducted an RCT at a university cancer center in China to evaluate the role of combination DC plus CIK immunotherapy as a maintenance treatment of advanced NSCLC. (34) From 2008 to 2010, 60 patients with stage IIIB or IV disease after treatment with 4 cycles of a platinum-based chemotherapy regimen were randomized into 2 groups. One group was treated with DC plus CIK cell therapy (n=30), and the control group received no adoptive immunotherapy (n=30). Outcome measures were PFS and adverse events of treatment. The PFS was 3.2 months in the DC plus CIK group (95% CI, 2.9 to 3.5 months) versus 2.6 months in the control group (95% CI, 2.39 to 2.73 months; p<.05). No significant toxic reactions were observed in the DC plus CIK group, including bone marrow toxicity and gastrointestinal reactions. The findings of this small single-center RCT would indicate that combination immunotherapy with dendritic and CIK cells may offer a viable option as maintenance therapy for patients with advanced NSCLC.

Observational Studies

Qi et al. (2024) conducted a matched cohort study of 128 patients with advanced NSCLC to evaluate DC plus CIK immunotherapy combined with chemoradiotherapy versus chemoradiotherapy alone. (44) The DC plus CIK group achieved a higher remission rate (85.9% vs. 65.6%, p<.05) and prolonged median survival (17 vs. 13 months, p<.05) compared to

chemoradiotherapy alone. Adverse events including fever, granulocytopenia, and gastrointestinal reactions occurred significantly less often in the DC-CIK group compared with controls (p<.01).

Subsection Summary: Non-Small-Cell Lung Cancer

Two RCTs, a cohort study, and a meta-analysis of these RCTs have evaluated the efficacy of DC plus CIK cells in NSCLC. The RCTs generally reported some benefits in response rates and/or survival. A matched-cohort study in advanced NSCLC found DC plus CIK added to chemoradiotherapy improved survival and remission rate as well as reduced toxicity versus chemoradiotherapy alone. Results of a meta-analysis of these trials also reported a statistically significant reduction in the hazard of death. However, the effect was inconsistent. Most were from Asia and did not use the standard of care as the control arm. This body of evidence is limited by the context of the studies (non-U.S.), small sample sizes, heterogeneous treatment groups, and other 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.

Medullary Thyroid Cancer

Observational Studies

In a phase 1 pilot study, Bachleitner-Hofman et al. (2009) reported on 10 patients with metastatic MTC treated with ADCs pulsed with allogeneic MTC tumor cell lysate. (45) At a median follow-up of 11 months, 3 (30%) patients had stable disease, and 7 (70%) patients progressed. No World Health Organization grade 3 or 4 toxicities or autoimmune reactions were observed. Of note, human leukocyte antigen match between patients and tumor cell lines did not predict disease stabilization or progression, suggesting that, should future studies demonstrate the efficacy of ADC therapy for MTC using allogeneic tumor lysate, an unlimited source of tumor material may be available for lysate preparation.

Subsection Summary: Medullary Thyroid Cancer

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

Pancreatic Cancer

Non-Randomized Controlled Trials

In a phase 1 study, Hirooka et al. (2009) assessed 5 patients with inoperable pancreatic cancer given reinfused ADCs and lymphokine-activated killer cells with gemcitabine; antigen priming of the ADCs was presumed to occur in vivo from apoptosis of gemcitabine-exposed tumor cells. (46) One patient had a partial response, 2 had stable disease for more than 6 months, and 2

had disease progression. Toxicities included grade 1 anemia and grade 2 leukocytopenia, nausea, and constipation.

van't Land et al. (2024) reported a single-center, open-label, single-arm phase I/II trial of ADC vaccination after pancreatectomy and standard-of-care therapy for pancreatic ductal adenocarcinoma. (47) Forty-three patients were screened and 38 were included in the primary analysis; ADCs were pulsed with an allogeneic mesothelioma tumor-cell lysate and administered in up to 5 vaccinations (74% completed all 5). The prespecified primary end point, 2-year recurrence-free survival (RFS) rate ≥ 60%, was met at a median follow-up of 25.5 months. Estimated 2-year RFS and OS were 64% and 83%, respectively. Vaccine-related toxicity was generally low grade (grade 1 in 97%, grade 2 in 18%, and 1 grade 3 dyspnea event); the most common adverse events were injection-site reactions (97%) and fever (68%).

Subsection Summary: Pancreatic Cancer
An open-label, single-arm phase I/II trial of ADC vaccination after pancreatectomy and standard therapy for pancreatic ductal adenocarcinoma met its prespecified 2-year recurrence-free survival endpoint with predominantly low-grade, vaccine-related adverse events. A small prospective noncomparative study in 5 patients with pancreatic cancer treated with ADCs and the lymphokine-activated killer has also been published. There are no RCTs comparing DC-based adoptive immunotherapy with the standard of care and therefore no conclusions can be made. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight and the use of an appropriate standard of care as the control arm showing treatment benefit.

GENETICALLY ENGINEERED T CELLS
Engineered T-cell–based antitumor immunotherapy uses gene transfer of tumor antigen-specific T-cell receptors (TCR) or synthetic chimeric antigen receptors. Review articles have highlighted recent progress in this field for solid and hematologic malignancies. (48-50)

T-Cell Receptor Therapy
Clinical Context and Therapy Purpose
The purpose of autologous peripheral T lymphocytes containing tumor antigen-specific TCRs is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with cancer.

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

Populations
The relevant population of interest is individuals with cancer.

Interventions
The therapy being considered is autologous peripheral T lymphocytes containing tumor antigen-specific TCRs.

Comparators
Comparators of interest include standard of care.

Outcomes
The general outcomes of interest are OS, DSS, QOL, treatment-related mortality, and treatment-related morbidity.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.
- The version of the therapeutic is described.
- Patient/sample clinical characteristics are described.
- Patient/sample selection criteria are described.

Systematic Reviews
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. (51) The analysis included data for 187 patients from 14 studies. Pooled objective response rates (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.

Observational Studies
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). (52) Nine (25%) patients experienced an objective response; 8 patients had a partial response lasting 3 months to more than 17 months, and 1 patient (in the gp100 group) had a CR lasting more than 14 months. Treatment toxicities included erythematous rash, anterior uveitis, hearing loss, and dizziness, suggesting that these were attributable to recognition by the genetically modified lymphocytes of normally quiescent cells expressing the targeted cancer antigens; melanocytic cells exist in the skin, eye, and the inner ear. Ideal targets for TCR gene therapy may be antigens that arise in cancers of nonessential organs (e.g., prostate, ovary, breast, thyroid) or are not expressed in normal adult tissues (e.g., cancer-testes antigens).

Additional studies have examined TCR gene therapy in Hodgkin (53) and non-Hodgkin lymphoma, (54) prostate tumors, (55) colon cancer, (56) and neuroblastoma. (57)

Section Summary: T-Cell Receptor 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 clear net health benefits with genetically engineered T cells in patients with metastatic melanoma.

Summary of Evidence

Cytotoxic T Lymphocytes

For individuals with Epstein-Barr virus (EBV)-associated cancers who receive cytotoxic T lymphocytes (CTL), the evidence includes 1 RCT and 2 small, prospective noncomparative cohort studies. Relevant outcomes are overall survival (OS), disease-specific survival (DSS), quality of life (QOL), and treatment-related mortality and morbidity. The RCT found no significant difference in OS or progression-free survival between patients with EBV-positive nasopharyngeal carcinoma treated with chemotherapy alone versus chemotherapy followed by CTL therapy. The cohort studies have shown a treatment response to infused CTL directed against cancer-associated viral antigens. To establish efficacy, the following are needed: large, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with *Cytomegalovirus*-associated cancers who receive CTL, the evidence includes a single case series. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. In the absence of a randomized controlled trial (RCT) comparing CTL with the standard of care, no conclusions can be made. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Cytotoxic-Induced Killer Cells

For individuals with nasopharyngeal carcinoma who receive cytotoxic-induced killer (CIK) cells, the evidence includes a single RCT. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The RCT reported a numerically favorable but statistically insignificant effect on progression-free survival (PFS) and OS. 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 renal cell carcinoma (RCC) who receive CIK cells, the evidence includes multiple RCTs. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The largest of the RCTs reported statistically significant gains in PFS and OS with CIK cell-based 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 other 2 RCTs have also reported response rates in favor of CIK therapy with an inconsistent effect on survival. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 (NSCLC) who receive CIK cells, the evidence includes multiple RCTs and a systematic review. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. A single systematic review of RCTs reported some benefits in efficacy and disease control rate. The trials assessed in the systematic review were limited by the context of the studies (non-U.S.), small sample sizes, heterogeneous treatment groups, and other 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.

Tumor-Infiltrating Lymphocytes

For individuals with EBV-associated nasopharyngeal carcinoma who receive tumor infiltrating lymphocytes (TILs), the evidence includes an RCT evaluating TILs as adjuvant therapy. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The RCT evaluating TILs as adjuvant therapy following standard chemoradiation in individuals with EBV-associated nasopharyngeal carcinoma found no difference in PFS or other clinical outcomes compared to patients who received standard chemoradiation alone. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Dendritic Cells

For individuals with glioblastoma multiforme who receive dendritic cells (DC), the evidence includes an RCT and a meta-analysis. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The meta-analysis of phase II and III trials, using open-label designs or external controls, found significant improvements in OS and progression-free survival across both newly diagnosed and recurrent populations, although with substantial heterogeneity in pooled outcomes and non-standardized vaccine manufacturing and administration. A Phase III externally controlled study of DC vaccination plus standard of care also reported longer OS in both newly diagnosed and recurrent disease, without a progression-free survival advantage. Given the reliance on non-propensity-matched external controls for OS estimates, causal inference remains limited. 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 NSCLC who receive DC, the evidence includes 2 RCTs, a cohort study, and a meta-analysis. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The RCTs have generally reported some benefits in response rates and/or survival. A matched-cohort study found improved survival and remission rates, as well as reduced toxicity, compared to chemoradiotherapy alone. The meta-analysis of these trials also reported a statistically significant reduction in the hazard of death. Most trials were from Asia and did not use the standard of care as the control arm. This body of evidence is limited by the context of the studies (non-U.S.), small sample sizes, heterogeneous treatment groups, and other 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 medullary thyroid cancer (MTC) who receive DC, the evidence includes 1 prospective noncomparative study. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. A small prospective noncomparative study in 10 MTC patients treated with autologous DC has been published. There are no RCTs comparing DC-based adoptive immunotherapy with the standard of care and, therefore, no conclusions can be made. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with pancreatic cancer who receive DC, the evidence includes 2 small prospective noncomparative studies. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. One study reported that it met its prespecified 2-year recurrence-free survival endpoint and observed predominantly low-grade, vaccine-related adverse safety events. The other study reported on treatment outcomes for only 5 patients with pancreatic cancer. Because of the noncomparative nature of the available evidence and small sample base, it is difficult to draw any meaningful conclusions. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

<u>Genetically Engineered T Cells</u>

Peripheral T Lymphocytes

For individuals with cancers who receive autologous peripheral T lymphocytes containing tumor antigen-specific T-cell receptors (TCRs), the evidence includes multiple small observational studies. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. Multiple observational studies have examined autologous peripheral T lymphocytes containing tumor antigen-specific TCRs in melanoma, Hodgkin and non-Hodgkin lymphoma, prostate

tumors, and neuroblastoma. Because of the noncomparative nature of the available evidence and small sample size, it is difficult to draw any meaningful conclusion. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

Current guidelines from the National Comprehensive Cancer Network do not include recommendations for adoptive immunotherapy to treat cancers of the bladder (58), central nervous system, (59) head and neck, (60) hepatobiliary system, (61, 62) kidney, (67) pancreatic, (63) stomach, (64) thyroid, (65) or non-small cell lung cancer. (66)

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 11.

Table 11. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Autologous Dendritic Cells			
NCT00338377	Lymphodepletion Plus Adoptive Cell Transfer with or without Dendritic Cell Immunization in Patients with Metastatic Melanoma	1230	Feb 2030
Dendritic Cells/Cytokine-Induced Killer Cells			
NCT02487992	The Randomized, Controlled, Multicenter Clinical Trial of CIK Plus S-1 and Bevacizumab as Maintenance Treatment for Patients With Advanced Colorectal Cancer	1200	Jul 2045
Dendritic cells/cytokine-induced killer cells			
NCT01691625	Concurrent Chemoradiation With or Without DC-CIK Immunotherapy in Treating Locally Advanced Esophageal Cancer	50	Dec 2021
Tumor-Infiltrating lymphocytes			
NCT01993719	A Phase II Study for Metastatic Melanoma Using High-Dose Chemotherapy Preparative Regimen Followed by Cell Transfer Therapy Using Tumor-Infiltrating Lymphocytes Plus IL-2 With the Administration of Pembrolizumab in the Retreatment Arm	33	Jul 2022

NCT: national clinical trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	36511, 37799, 96365
HCPCS Codes	S2107

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
12/15/2025	Document updated. Coverage unchanged. Added references 10, 11, 26, 32, 39, 40, 44, 47 and 56; others updated and some removed.
02/01/2025	Document updated with literature review. Coverage unchanged. Added references 4, 20, 25, 44, 53, and 54; others updated and some removed.
01/01/2024	Reviewed. No changes.
01/01/2023	Document updated with literature review. Coverage unchanged. Added/updated the following references: 1-3 and 47-56.
02/01/2022	Reviewed. No changes.
03/15/2021	Document updated with literature review. Editorial changes made to Coverage without change to intent. References 3-5, 15, 17 and 20 added; some references updated, others removed.
12/15/2020	Review only. No changes.
07/01/2019	Document updated with literature review. Coverage unchanged. References 12-15 and 35 added; several removed.
12/15/2017	Document updated with literature review. Coverage unchanged. The following note has been placed in the coverage section: NOTE 3: See RX501.088 Chimeric Antigen Receptor (CAR) T-cell Therapy regarding genetically engineered T-cells.
04/15/2016	Reviewed. No changes.
06/01/2015	Document updated with literature review. The following examples were added to the experimental, investigational and unproven statement: Cytotoxic T lymphocytes, (CTL) and Genetically Engineered - cells.
07/01/2014	Reviewed. No changes.
10/01/2013	Document updated with literature review. The following example was added to the experimental, investigational and unproven statement: Cytokine-induced killer (CIK) cells.
11/15/2011	Document updated with literature review. Coverage unchanged. Adoptive immunotherapy remains experimental, investigational and unproven. List of examples of adoptive immunotherapy was revised.
07/01/2009	Revised and updated with literature review, no coverage change.
08/01/2007	Revised/Updated Entire Document

07/15/2004	Revised/Updated Entire Document
06/01/1999	Revised/Updated Entire Document
11/01/1998	New Medical Document