



BlueCross BlueShield  
of Alabama

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**Name of Blue Advantage Policy:**  
**Adoptive Immunotherapy**

Policy #: 105  
Category: Therapy

Latest Review Date: October 2020  
Policy Grade: B

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**BACKGROUND:**

*Blue Advantage medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational\*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
  - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
  - *Furnished in a setting appropriate to the patient's medical needs and condition;*
  - *Ordered and furnished by qualified personnel;*
  - *One that meets, but does not exceed, the patient's medical need; and*
  - *At least as beneficial as an existing and available medically appropriate alternative.*

*\*Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill **Original Medicare** for covered services that are related to **clinical trials** that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

## **POLICY:**

### **Effective for dates of service on or after July 1, 2005:**

**Blue Advantage** will treat all adoptive immunotherapy techniques intended to enhance autoimmune effects as a **non-covered benefit** and as **investigational** for all indications.

**Note:** CAR-T Therapy is addressed separately in **Decision Memo for Chimeric Antigen Receptor (CAR) T-cell Therapy for Cancers (CAG-00451N)**.

**Note:** Allogeneic stem-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 stem-cell transplantation relies on a donor-versus-malignancy effect of donor lymphocytes, while the adoptive immunotherapy techniques described in this policy enhance autoimmune effects primarily. The use of RIC in stem-cell transplantation is discussed for specific cancers in individual policies related to stem-cell transplantation.

*Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.*

## **DESCRIPTION OF PROCEDURE OR SERVICE:**

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.

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 (LAK) cells and activating them in vitro with the T-cell growth factor interleukin-2 (IL-2) and other cytokines. More recent techniques yield 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. Cytokine-induced killer (CIK) cells have recently been recognized as a new type of anti-tumor effector cells, which can proliferate rapidly in vitro, with stronger anti-tumor activity and broader spectrum of targeted tumor than other reported anti-tumor effector cells.

### **Cellular Therapy and Dendritic Cell Infusions**

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

ACT 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 (ELISA)
4. lymphodepletion of the host with immunosuppressive agents
5. adoptive transfer (i.e., transfusion) of lymphocytes back into the tumor-bearing host

Dendritic cell-based immunotherapy uses autologous dendritic cells (ADC) to activate a lymphocyte-mediated cytotoxic response against specific antigens in vivo. ADCs harvested from the patient are either pulsed with antigen or transfected with a viral vector bearing a common cancer antigen. The activated ADCs are then transfused back into the patient, where they present antigen to effector lymphocytes (CD4+ T cells, CD8+ 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 further regulate the host immune system, recent protocols use various cytokines (e.g., IL-7 and IL-15 instead of IL-2) to propagate lymphocytes. Protocols also differ in the extent of host lymphodepletion induced prior to transfusing the lymphocytes to the tumor-bearing host.

### **KEY POINTS:**

The most recent literature search was performed through August 31, 2020.

## **Summary**

### **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- $\alpha$ -2. This body of evidence is limited by the context of the studies (non-U.S.) and choice of a nonstandard comparator. The other 2 RCTs have also reported response rates in favor of CIK therapy with inconsistent effect on survival. To establish efficacy, the following is needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with gastric cancer who receive CIK cells, the evidence includes 2 meta-analyses encompassing non-randomized trials. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Both meta-analyses reported statistically significant effect on disease-free survival, overall survival, quality of life, and progression free 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 and one meta-analysis. 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. A meta-analysis that included both gastric cancer and CRC found improvements in OS and PFS in favor of CIK/DC-CIK compared to chemotherapy alone. To establish efficacy, the following is needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. 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 meta-analyses that include RCTs and quasi-randomized trials. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Meta-analyses of these trials have reported improved overall survival 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 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 meta-analysis of randomized and non-randomized trials. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The meta-analysis evaluating TIL with IL-2 in patients with cutaneous melanoma reported a ORR of 41%. Pooled 1-year overall survival rates ranged from 46.1% to 56.5% depending on the IL-2 dose level. 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.

### **Practice Guidelines and Position Statements**

Current clinical practice guidelines from the National Comprehensive Cancer Network (NCCN) do not include recommendations for adoptive immunotherapy to treat cancers of the bladder central nervous system, head and neck, hepatobiliary system, kidney, pancreas, stomach, or thyroid; melanoma, or non-small cell lung cancer.

### **U.S. Preventive Services Task Force Recommendations**

The U.S. Preventive Services Task Force has not addressed the treatment of adoptive immunotherapy.

### **KEY WORDS:**

Adoptive immunotherapy (AI), lymphokine-activated killer (LAK) cell therapy, tumor-infiltrating lymphocyte (TIL) therapy, autolymphocyte therapy (ALT), leukopheresis, and interleukin-2 (IL-2), cytotoxic T-lymphocytes, genetically engineered T-cells, cytokine-induced killer cells, T-Cell Receptor Therapy, TCR, adoptive cellular therapy, ACT, CIK, antigen-loaded autologous dendritic cells, ADC.

### **APPROVED BY GOVERNING BODIES:**

Adoptive immunotherapy is not a U.S. Food and Drug Administration (FDA)-regulated procedure.

### **BENEFIT APPLICATION:**

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

### **CURRENT CODING:**

#### **HCPCS codes:**

**S2107** Adoptive immunotherapy, i.e., development of specific anti-tumor reactivity (e.g., tumor infiltrating lymphocyte therapy) per course of treatment

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## **POLICY HISTORY:**

Adopted for Blue Advantage, March 2005

Available for comment May 1-June 14, 2005

Medical Policy Group, April 2007

Medical Policy Group, January 2009

Medical Policy Group, June 2011

Medical Policy Group, March, 2012

Medical Policy Group, September 2013

Medical Policy Group, January 2014

Medical Policy Group, December 2014

Medical Policy Group, January 2016

Medical Policy Group, March 2016

Medical Policy Group, August 2017

Medical Policy Group, October 2017

Medical Policy Group, November 2017

Medical Policy Group, December 2017

Medical Policy Group, August 2018 **(2)**: Updates to Key Points and References; no change in policy statement.

Medical Policy Group, March 2019

Medical Policy Group, November 2019

Medical Policy Group, October 2020

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*This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.*

*This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.*