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MEDICAL POLICY – 8.01.01

Adoptive Immunotherapy

BCBSA Ref. Policy:	8.01.01
Effective Date:	May 1, 2025
Last Revised:	Apr. 21, 2025
Replaces:	N/A

RELATED MEDICAL POLICIES:

8.01.53	Cellular Immunotherapy for Prostate Cancer
8.01.63	Chimeric Antigen Receptor Therapy for Hematologic Malignancies
8.01.520	Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

Clicking this icon returns you to the hyperlinks menu above.

Introduction

The immune system is made up of several different disease-fighting cells. When someone has cancer, their immune system sometimes doesn't work as it should. Adoptive immunotherapy is a treatment that uses the person's own immune cells in order to destroy cancer. Specific types of immune system cells are withdrawn from the person to be treated. They're modified in a lab and then given back to the individual. Adoptive immunotherapy is being studied.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Treatment	Investigational
Other applications	**All adoptive immunotherapy techniques intended to enhance autoimmune effects are considered investigational 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.** **The treatments listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.**

Coding

Code	Description
CPT	
36511	Therapeutic apheresis; for white blood cells
HCPCS	
S2107	Adoptive immunotherapy i.e., development of specific antitumor reactivity (e.g., tumor-infiltrating lymphocyte therapy) per course of treatment

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

N/A

Evidence Review

Description

The spontaneous regression of certain cancers (e.g., renal cell carcinoma, melanoma) supports the idea that an individual'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 an individual'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 individual, processed for some period of time, and then infused back into the individual.

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 US-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 US-born Hispanic individuals.

Based on data from 2015 through 2019, kidney cancer is more common in men than women and occurs more often in American Indian and Alaskan Native individuals, followed by Black individuals.[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 individuals with localized kidney cancer from the National Cancer Database between 2010 and 2017.[3] Investigators found that that female individuals were treated more aggressively compared with male individuals, with lower adjusted odds of undertreatment and higher adjusted odds of overtreatment. They also found that Black and Hispanic individuals had higher adjusted odds of undertreatment, and overtreatment compared to White individuals, 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 individuals.

Adoptive Immunotherapy

Adoptive immunotherapy uses "activated" lymphocytes as a treatment modality. 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-2 (IL-2) and other cytokines. More recent techniques have yielded select populations of cytotoxic T lymphocytes with specific reactivity to tumor antigens. Peripheral lymphocytes are propagated in vitro with antigen-presenting dendritic cells (DC) that have been pulsed with tumor antigens. Alternatively, innate tumor-infiltrating lymphocytes (TIL) from the tumor biopsy are propagated in vitro with interleukin-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 cells have been recognized as a new type of anti-tumor effector cells, which can proliferate rapidly in vitro, with stronger anti-tumor activity and a broader spectrum of targeted tumors than other reported anti-tumor effector cells.[4]

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 individuals. In current trials, two methods are studied: adoptive cellular therapy and antigen-loaded dendritic cell infusions.

Adoptive cellular therapy is "the administration of an individual's own (autologous) or donor (allogeneic) anti-tumor lymphocytes following a lymphodepleting preparative regimen."[5] Protocols vary, but include these common steps:

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

Dendritic cell-based immunotherapy uses autologous DC (ADC) to activate a lymphocyte-mediated cytotoxic response against specific antigens in vivo. ADCs harvested from the individual are either pulsed with antigen or transfected with a viral vector bearing a common cancer antigen. The activated ADCs are then re-transfused back into the individual, where they present antigen to effector lymphocytes (CD4-positive T cells, CD8-positive T cells, and in some cases, B cells). This initiates a cytotoxic response against the antigen and against any cell expressing the antigen. In cancer immunotherapy, ADCs are pulsed with tumor antigens; effector lymphocytes then mount a cytotoxic response against tumor cells expressing these antigens (see **Related Policies** for dendritic cell-based immunotherapy for prostate cancer).

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 interleukin -2) to propagate lymphocytes. Protocols also differ in the extent of host lymphodepletion induced prior to transfusing lymphocytes to the tumor-bearing host.

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

Chimeric antigen receptor T-cell therapies for certain hematologic malignancies (e.g., tisagenlecleucel, axicabtagene ciloleucel) are discussed in a separate policy (see **Related Policies** above).

Summary of Evidence

Cytotoxic T Lymphocytes

For individuals with Epstein-Barr virus (EBV)-associated cancers who receive cytotoxic T lymphocytes (CTL), the evidence includes two small, prospective noncomparative cohort studies. The 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 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. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. In the absence of an 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 CIK cells, the evidence includes a single RCT. The 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 (PFS) and overall 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 renal cell carcinoma (RCC) who receive CIK cells, the evidence includes multiple RCTs. The 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 (IL)-2 plus interferon-α-2. This body of evidence is limited by the context of the studies (non-US) and choice of a nonstandard comparator. The other two RCTs have also reported response rates in favor of CIK therapy with 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, disease-free survival (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 who receive CIK cells, the evidence includes a single RCT and one cohort study. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Results of the RCT showed a statistically significant effect on overall survival in favor of immunotherapy vs chemotherapy alone. To establish efficacy, the following 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 who receive CIK cells, the evidence includes several RCTs. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Several RCTs from Asia have generally reported some benefits in response rates and/or survival. The results of a meta-analysis of these trials have also shown a statistically significant 41% reduction in the hazard of death, but there was considerable heterogeneity across the included studies. This body of evidence is limited by the context of the studies (non-US), small sample sizes, heterogeneous treatment groups, and other methodologic 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. The 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 trials assessed in the systematic review were limited by the context of the studies (non-US), small sample sizes, heterogeneous treatment groups, and other methodologic 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 melanoma who receive tumor infiltrating lymphocytes (TILs), the evidence includes a meta-analysis of randomized trials. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The meta-analysis evaluating TIL with IL-2 in individuals with cutaneous melanoma reported an objective response rate of 41%. Pooled 1-year OS rates ranged from 46.1% to 56.5% depending on the IL-2 dose level. 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 EBV-associated nasopharyngeal carcinoma who receive 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 individuals 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 a systematic review of observational studies. The 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 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. Interim results from one such RCT have been published but are not informative because the individuals were unblinded and results combined for the treatment and placebo arms. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with non-small-cell lung cancer who receive dendritic cells, the evidence includes two RCTs and a meta-analysis. The 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 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 standard of care as the control arm. This body of evidence is limited by the context of the studies (non-US), small sample sizes, heterogeneous treatment groups, and other methodologic 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 who receive dendritic cells, the evidence includes one prospective noncomparative study. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. A small prospective noncomparative study in ten medullary thyroid cancer individuals 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 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 dendritic cells, the evidence includes a small prospective noncomparative study. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The study reported on treatment outcomes for five individuals 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.

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. The 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 and a 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.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in **Table 1**.

Table 1. Summary of Ongoing Trial

NCT No.	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
NCT01204684	A Phase II Clinical Trial Evaluating Autologous Dendritic Cells Pulsed With Tumor Lysate Antigen +/- Toll-like Receptor Agonists for the Treatment of Malignant Glioma	60	Jan 2025
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

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

Table 2. Summary of Unpublished Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
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
Dendritic cells/cytokine-induced killer cells			
NCT01691625	Concurrent Chemoradiation With or Without DC-CIK Immunotherapy in Treating Locally Advanced Esophageal Cancer	50	Dec 2021

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

Practice Guidelines and Position Statements

Current guidelines from the National Comprehensive Cancer Network do not include recommendations for adoptive immunotherapy to treat cancers of the bladder,[44] central nervous system,[44] head and neck,[44] hepatobiliary system,[44] kidney,[44] pancreatic,[45] stomach,[46] thyroid,[47] melanoma,[48] or non-small-cell lung cancer.[49]

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

References

1. Singh SK, Singh R. Liver cancer incidence and mortality: Disparities based on age, ethnicity, health and nutrition, molecular factors, and geography. Cancer Health Disparities. Mar 2020; 4: e1-e10. PMID 34164612
2. National Cancer Institute. SEER Cancer Stat Facts: Kidney and Renal Pelvis Cancer. 2022. **https://seer.cancer.gov/statfacts/html/kidrp.html**. Accessed April 7, 2025.
3. Howard JM, Nandy K, Woldu SL, et al. Demographic Factors Associated With Non-Guideline-Based Treatment of Kidney Cancer in the United States. JAMA Netw Open. Jun 01 2021; 4(6): e2112813. PMID 34106265
4. Hontscha C, Borck Y, Zhou H, et al. Clinical trials on CIK cells: first report of the international registry on CIK cells (IRCC). J Cancer Res Clin Oncol. Feb 2011; 137(2): 305-10. PMID 20407789
5. Rosenberg SA, Restifo NP, Yang JC, et al. Adoptive cell transfer: a clinical path to effective cancer immunotherapy. Nat Rev Cancer. Apr 2008; 8(4): 299-308. PMID 18354418
6. Tang X, Liu T, Zang X, et al. Adoptive cellular immunotherapy in metastatic renal cell carcinoma: a systematic review and meta-analysis. PLoS One. 2013; 8(5): e62847. PMID 23667530
7. Xie F, Zhang X, Li H, et al. Adoptive immunotherapy in postoperative hepatocellular carcinoma: a systemic review. PLoS One. 2012; 7(8): e42879. PMID 22916174
8. Zhong JH, Ma L, Wu LC, et al. Adoptive immunotherapy for postoperative hepatocellular carcinoma: a systematic review. Int J Clin Pract. Jan 2012; 66(1): 21-7. PMID 22171902
9. Bollard CM, Gottschalk S, Torrano V, et al. Sustained complete responses in patients with lymphoma receiving autologous cytotoxic T lymphocytes targeting Epstein-Barr virus latent membrane proteins. J Clin Oncol. Mar 10 2014; 32(8): 798-808. PMID 24344220
10. Chia WK, Teo M, Wang WW, et al. Adoptive T-cell transfer and chemotherapy in the first-line treatment of metastatic and/or locally recurrent nasopharyngeal carcinoma. Mol Ther. Jan 2014; 22(1): 132-9. PMID 24297049
11. Ohtani T, Yamada Y, Furuhashi A, et al. Activated cytotoxic T-lymphocyte immunotherapy is effective for advanced oral and maxillofacial cancers. Int J Oncol. Nov 2014; 45(5): 2051-7. PMID 25120101

12. Schuessler A, Smith C, Beagley L, et al. Autologous T-cell therapy for cytomegalovirus as a consolidative treatment for recurrent glioblastoma. Cancer Res. Jul 01 2014; 74(13): 3466-76. PMID 24795429

13. Li JJ, Gu MF, Pan K, et al. Autologous cytokine-induced killer cell transfusion in combination with gemcitabine plus cisplatin regimen chemotherapy for metastatic nasopharyngeal carcinoma. J Immunother. Feb-Mar 2012; 35(2): 189-95. PMID 22306907

14. Liu L, Zhang W, Qi X, et al. Randomized study of autologous cytokine-induced killer cell immunotherapy in metastatic renal carcinoma. Clin Cancer Res. Mar 15 2012; 18(6): 1751-9. PMID 22275504

15. Zhang Y, Wang J, Wang Y, et al. Autologous CIK cell immunotherapy in patients with renal cell carcinoma after radical nephrectomy. Clin Dev Immunol. 2013; 2013: 195691. PMID 24382970

16. Zhao X, Zhang Z, Li H, et al. Cytokine induced killer cell-based immunotherapies in patients with different stages of renal cell carcinoma. Cancer Lett. Jul 01 2015; 362(2): 192-8. PMID 25843292

17. Wang X, Tang S, Cui X, et al. Cytokine-induced killer cell/dendritic cell-cytokine-induced killer cell immunotherapy for the postoperative treatment of gastric cancer: A systematic review and meta-analysis. Medicine (Baltimore). Sep 2018; 97(36): e12230. PMID 30200148

18. Du H, Yang J, Zhang Y. Cytokine-induced killer cell/dendritic cell combined with cytokine-induced killer cell immunotherapy for treating advanced gastrointestinal cancer. BMC Cancer. Apr 28 2020; 20(1): 357. PMID 32345239

19. Zhao H, Wang Y, Yu J, et al. Autologous Cytokine-Induced Killer Cells Improves Overall Survival of Metastatic Colorectal Cancer Patients: Results From a Phase II Clinical Trial. Clin Colorectal Cancer. Sep 2016; 15(3): 228-35. PMID 27052743

20. Cao J, Kong FH, Liu X, et al. Immunotherapy with dendritic cells and cytokine-induced killer cells for hepatocellular carcinoma: A meta-analysis. World J Gastroenterol. Jul 21 2019; 25(27): 3649-3663. PMID 31367163

21. Cai XR, Li X, Lin JX, et al. Autologous transplantation of cytokine-induced killer cells as an adjuvant therapy for hepatocellular carcinoma in Asia: an update meta-analysis and systematic review. Oncotarget. May 09 2017; 8(19): 31318-31328. PMID 28412743

22. Wang M, Cao JX, Pan JH, et al. Adoptive immunotherapy of cytokine-induced killer cell therapy in the treatment of non-small cell lung cancer. PLoS One. 2014; 9(11): e112662. PMID 25412106

23. Dafni U, Michielin O, Lluesma SM, et al. Efficacy of adoptive therapy with tumor-infiltrating lymphocytes and recombinant interleukin-2 in advanced cutaneous melanoma: a systematic review and meta-analysis. Ann Oncol. Dec 01 2019; 30(12): 1902-1913. PMID 31566658

24. Timmerman JM, Czerwinski DK, Davis TA, et al. Idiotype-pulsed dendritic cell vaccination for B-cell lymphoma: clinical and immune responses in 35 patients. Blood. Mar 01 2002; 99(5): 1517-26. PMID 11861263

25. Lacy MQ, Wettstein P, Gastineau DA, et al. Dendritic cell-based idiotype vaccination in post transplant multiple myeloma [abstract]. Blood. 1999;94(10 supp part 1):122a.

26. Motta MR, Castellani S, Rizzi S, et al. Generation of dendritic cells from CD14+ monocytes positively selected by immunomagnetic adsorption for multiple myeloma patients enrolled in a clinical trial of anti-idiotype vaccination. Br J Haematol. Apr 2003; 121(2): 240-50. PMID 12694245

27. Triozzi PL, Khurram R, Aldrich WA, et al. Intratumoral injection of dendritic cells derived in vitro in patients with metastatic cancer. Cancer. Dec 15 2000; 89(12): 2646-54. PMID 11135227

28. Bedrosian I, Mick R, Xu S, et al. Intranodal administration of peptide-pulsed mature dendritic cell vaccines results in superior CD8+ T-cell function in melanoma patients. J Clin Oncol. Oct 15 2003; 21(20): 3826-35. PMID 14551301

29. Shi SB, Ma TH, Li CH, et al. Effect of maintenance therapy with dendritic cells: cytokine-induced killer cells in patients with advanced non-small cell lung cancer. Tumori. May-Jun 2012; 98(3): 314-9. PMID 22825506

30. Yang L, Ren B, Li H, et al. Enhanced antitumor effects of DC-activated CIKs to chemotherapy treatment in a single cohort of advanced non-small-cell lung cancer patients. Cancer Immunol Immunother. Jan 2013; 62(1): 65-73. PMID 22744010

31. Su Z, Dannull J, Heiser A, et al. Immunological and clinical responses in metastatic renal cancer patients vaccinated with tumor RNA-transfected dendritic cells. Cancer Res. May 01 2003; 63(9): 2127-33. PMID 12727829

32. Santin AD, Bellone S, Palmieri M, et al. Induction of tumor-specific cytotoxicity in tumor infiltrating lymphocytes by HPV16 and HPV18 E7-pulsed autologous dendritic cells in patients with cancer of the uterine cervix. Gynecol Oncol. May 2003; 89(2): 271-80. PMID 12713991

33. Tanyi JL, Chu CS. Dendritic cell-based tumor vaccinations in epithelial ovarian cancer: a systematic review. Immunotherapy. Oct 2012; 4(10): 995-1009. PMID 23148752

34. Bregy A, Wong TM, Shah AH, et al. Active immunotherapy using dendritic cells in the treatment of glioblastoma multiforme. Cancer Treat Rev. Dec 2013; 39(8): 891-907. PMID 23790634

35. Liau LM, Ashkan K, Tran DD, et al. First results on survival from a large Phase 3 clinical trial of an autologous dendritic cell vaccine in newly diagnosed glioblastoma. J Transl Med. May 29 2018; 16(1): 142. PMID 29843811

36. Chen R, Deng X, Wu H, et al. Combined immunotherapy with dendritic cells and cytokine-induced killer cells for malignant tumors: a systematic review and meta-analysis. Int Immunopharmacol. Oct 2014; 22(2): 451-64. PMID 25073120

37. Bachleitner-Hofmann T, Friedl J, Hassler M, et al. Pilot trial of autologous dendritic cells loaded with tumor lysate(s) from allogeneic tumor cell lines in patients with metastatic medullary thyroid carcinoma. Oncol Rep. Jun 2009; 21(6): 1585-92. PMID 19424640

38. Hirooka Y, Itoh A, Kawashima H, et al. A combination therapy of gemcitabine with immunotherapy for patients with inoperable locally advanced pancreatic cancer. Pancreas. Apr 2009; 38(3): e69-74. PMID 19276867

39. Ngo MC, Rooney CM, Howard JM, et al. Ex vivo gene transfer for improved adoptive immunotherapy of cancer. Hum Mol Genet. Apr 15 2011; 20(R1): R93-9. PMID 21415041

40. Ochi T, Fujiwara H, Yasukawa M. Requisite considerations for successful adoptive immunotherapy with engineered T-lymphocytes using tumor antigen-specific T-cell receptor gene transfer. Expert Opin Biol Ther. Jun 2011; 11(6): 699-713. PMID 21413911

41. Humphries C. Adoptive cell therapy: Honing that killer instinct. Nature. Dec 19 2013; 504(7480): S13-5. PMID 24352359

42. Johnson LA, Morgan RA, Dudley ME, et al. Gene therapy with human and mouse T-cell receptors mediates cancer regression and targets normal tissues expressing cognate antigen. Blood. Jul 16 2009; 114(3): 535-46. PMID 19451549

43. Savoldo B, Rooney CM, Di Stasi A, et al. Epstein Barr virus specific cytotoxic T lymphocytes expressing the anti-CD30zeta artificial chimeric T-cell receptor for immunotherapy of Hodgkin disease. Blood. Oct 01 2007; 110(7): 2620-30. PMID 17507664

44. Till BG, Jensen MC, Wang J, et al. Adoptive immunotherapy for indolent non-Hodgkin lymphoma and mantle cell lymphoma using genetically modified autologous CD20-specific T cells. Blood. Sep 15 2008; 112(6): 2261-71. PMID 18509084

45. Pinthus JH, Waks T, Malina V, et al. Adoptive immunotherapy of prostate cancer bone lesions using redirected effector lymphocytes. J Clin Invest. Dec 2004; 114(12): 1774-81. PMID 15599402

46. Pule MA, Savoldo B, Myers GD, et al. Virus-specific T cells engineered to coexpress tumor-specific receptors: persistence and antitumor activity in individuals with neuroblastoma. Nat Med. Nov 2008; 14(11): 1264-70. PMID 18978797

47. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: bladder cancer. Version 1.2025. Updated March 25, 2025. **http://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf**. Accessed April 7, 2025.

48. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: central nervous system cancers. Version 1.2023. Updated March 24, 2023. **http://www.nccn.org/professionals/physician_gls/pdf/cns.pdf**. Accessed April 7, 2025.

49. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: head and neck cancers. Version 5.2024. Updated March 18, 2025. **http://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf**. Accessed April 7, 2025.

50. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: hepatocellular carcinoma. Version 1.2025. Updated March 20, 2025. **http://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf**. Accessed April 7, 2025.

51. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: pancreatic adenocarcinoma. Version 2.2025. Updated February 3, 2025. **http://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf**. Accessed April 7, 2025.

52. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: gastric cancer. Version 2.2025. Updated April 4, 2025. **http://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf**. Accessed April 7, 2025.

53. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: thyroid carcinoma. Version 1.2025. Updated March 27, 2025. **http://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf**. Accessed April 7, 2025.

54. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: cutaneous melanoma. Version 2.2025. Updated January 28, 2025. **https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf**. Accessed April 7, 2025.

55. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: non-small cell lung cancer. Version 3.2025. Updated January 14, 2025. **http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf**. Accessed April 7, 2025.

History

Date	Comments
01/97	Add to Therapy Section - New Policy
05/19/98	Replace policy. Policy updated; new indications
12/10/02	Replace policy. Policy updated; new references added. No change in policy statement.
04/15/03	Replace policy. Policy reviewed with CPT codes added. No change in policy statement.
01/01/04	Replace policy. CPT code updates only.
05/11/04	Replace policy. Policy updated; no change in policy statement. Additional discussion of dendritic cell therapy.
06/14/05	Replace policy. Policy updated with literature search; no change in policy statement.
02/06/06	Codes Updated. No other changes.
06/16/06	Replace policy. Policy updated with literature search; no change in policy statement; Scope and Disclaimer updated.
06/12/07	Replace policy. Policy updated; no change in policy statement. Reviewed and recommended by OAP on May 24, 2007.
01/13/09	Replace policy. Policy updated with literature search. Policy statement updated to included "adoptive cellular therapy (ACT) for the administration of lymphokine-activated killer cells (LAK) tumor-infiltrating lymphocytes (TIL), or antigen-loaded

Date	Comments
	dendritic cells (ADCs)" as an investigational indication. Investigational statement deleted. References added. Reviewed and recommended by OAP on August 21, 2008.
12/08/09	Cross Reference Update - No other changes.
05/11/10	Cross Reference Update - No other changes.
06/13/11	Replace policy. Policy updated with literature search; reference numbers 33–48 added; no change in policy statements. ICD-10 codes added to policy.
02/14/12	Replace policy. Policy updated with literature search; references 23 and 24 added and other references renumbered or removed. No change in policy statements.
08/15/12	Update Related Policies: remove 2.03.04, as it was archived.
09/28/12	Update Coding Section – ICD-10 codes are now effective 10/01/2014.
02/13/13	Replace policy. Policy updated with literature search; Two systematic reviews added; Primary studies added on cytokine-induced killer (CIK) cells; references 1, 3-6, 24, and 27 added and other references renumbered. The wording of the policy statement under adoptive cellular therapy was changed to include cytokine-induced killer (CIK) cells; however, the intent of both policy statements (i.e., investigational) is unchanged. Remove Related Policy 2.03.500 as it was archived.
07/25/13	Update Related Policies. Add 8.01.520.
02/24/14	Replace policy. Policy updated with literature search through November 8, 2013; references 3, 8, 27, and 31 added. No change in policy statements.
02/25/15	Annual Review. Policy updated with literature review through November 2, 2014; references 6-9, 12, 14-17, 41, 46, 52-53, and 56-65 added; reference 55 updated. Rationale reorganized and references renumbered. Cytotoxic T-lymphocytes and genetically engineered T cells added to investigational policy statements; "autologous" added to clarify antigen-loaded dendritic cells. ICD-9 and ICD-10 codes removed; these are not utilized in policy adjudication.
02/09/16	Annual Review. Policy updated with literature review through November 10, 2015; references 13 and 17-18 added. Section on lymphokine-activated killer cell deleted as this is an obsolete intervention. Policy statements unchanged.
01/01/18	Annual Review, approved December 12, 2017. Policy updated with literature review through April 2017. Policy statement changed for clarity as Kymriah™ (tisagenlecleucel) and Yescarta™ (axicabtagene ciloleucel) are addressed in policy 5.01.580. Removed codes 96365, 96367, 96368, and S2107.
11/01/18	Annual Review, approved October 19, 2018. Policy criteria for Chimeric Antigen Receptor (CAR) T Cell Therapies is now addressed in this policy; added codes J3590, Q2040, Q2041, S2107. Removed CPT code 37799. Policy 5.01.580 is now deleted. Policy updated with literature review through June 2018; several references added.
11/17/18	Minor update, added Documentation Requirements section.

Date	Comments
01/01/19	Coding update, added 0537T, 0538T, 0539T, 0540T, and Q2042 (new codes effective 1/1/19).
04/01/19	Annual Review, approved March 19, 2019. Policy updated with literature review through October 2018; reference 31 added. Policy statements unchanged.
01/01/20	Coding update, removed HCPCS code Q2040 as it terminated 1/1/19.
07/01/20	Annual Review, approved June 9, 2020. Statements regarding use of tisagenlecleucel and axicabtagene ciloleucel were removed and added to new policy 8.01.63 Chimeric Antigen Receptor Therapy for Hematologic Malignancies, references updated. Policy Coverage section revised to 'Other applications of adoptive immunotherapy not addressed in Related Policy 8.01.63 Chimeric Antigen Receptor Therapy for Hematologic Malignancies are considered investigational'. Removed codes 0537T, 0538T, 0539T, 0540T, Q2041 and Q2042.
12/01/20	Interim Review, approved November 19, 2020. No changes to Coverage Criteria. Updated Evidence Review and References.
12/01/21	Annual Review, approved November 18, 2021. Policy updated with literature review through August 24, 2021; references updated. Policy section revised to "All adoptive immunotherapy techniques intended to enhance autoimmune effects are considered investigational for the indications included, but not limited to" as referenced in this policy.
01/01/23	Annual Review, approved December 23, 2022. Policy updated with literature review through August 24, 2022; references added. Policy statements unchanged. Changed the wording from "patient" to "individual" throughout the policy for standardization.
01/01/24	Annual Review, approved December 11, 2023. Policy updated with literature review through August 11, 2023; references added. Indication added (TIL in EBV-associated nasopharyngeal carcinoma). Policy statements unchanged.
09/01/24	Annual Review, approved August 26, 2024. No changes to policy statements.
05/01/25	Annual Review, approved April 21, 2025. Clarified that the treatments listed in this policy are subject to the product's FDA dosage and administration prescribing information.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to

the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.