FEP Medical Policy Manual

FEP 8.01.01 Adoptive Immunotherapy

Effective Policy Date: January 1, 2021

Original Policy Date: September 2011

Related Policies:

5.21.101 Kymriah
5.21.105 Yescarta
5.21.130 Xpovio
5.90.33 Luxturna
8.01.53 - Cellular Immunotherapy for Prostate Cancer

Adoptive Immunotherapy

Description

The spontaneous regression of certain cancers (eg, 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

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 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 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.[1,]

Cellular Therapy and Dendritic Cell (DC) 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.”[2,] 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 (ie, transfusion) of lymphocytes back into the tumor-bearing host.

DC-based immunotherapy uses autologous DC (ADC) to activate a lymphocyte-mediated cytotoxic response against specific antigensin vivo. ADCs harvested from the patient is 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. (See evidence review 8.01.53 for a discussion of DC-based immunotherapy for prostate cancer.)

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

OBJECTIVE

The objective of this evidence review is to assess whether the use of adoptive immunotherapy in patients with various malignancies improves the net health outcome. Policies 5.21.101 (Kymriah), 5.21.105 (Yescarta) and 5.21.130 (Xpovio) address the use of these genetically engineered T cells. Policy 5.90.33 (Luxturna) addresses the use of genetic therapy for confirmed biallelic RPE65 mutation-associated retinal dystrophy. This policy does not address those FDA approved products.

POLICY STATEMENT

All adoptive immunotherapy techniques intended to enhance autoimmune effects are considered **investigational** for the indications included, but not limited to, cancers associated with EBV, CMV, nasopharyngeal cancer, renal cell carcinoma, gastric cancer, colorectal cancer, hepatocellular carcinoma, NSCLC, 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

Chimeric antigen receptor T-cell therapies for certain hematologic malignancies (eg, tisagenlecleucel, axicabtagene ciloleucel, brexucabtagene autoleucel) are discussed separately in Policies 5.21.101 (Kymriah), 5.21.105 (Yescarta) and 5.21.130 (Xpovio).

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Adoptive immunotherapy is a specialized service that may require an out-of-network referral.

FDA REGULATORY STATUS

The FDA has granted Orphan Drug designation/approval to multiple natural killer cell and dendritic cell products for the treatment of cancers such as of Merkel cell carcinoma, multiple myeloma, acute myeloid leukemia, malignant glioma, hepatocellular carcinoma, pancreatic cancer, glioblastoma and others.

RATIONALE

Summary of Evidence

Cytotoxic T Lymphocytes

For individuals with Epstein-Barr virus-associated cancers who receive cytotoxic T lymphocytes (CTL), the evidence includes 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 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 the effects of the technology on health outcomes.

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 the effects of the technology on health outcomes.

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 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 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 OS, DSS, QOL, and treatment-related mortality and morbidity. The largest of the RCTs reported statistically significant gains in progression-free survival and OS with CIK cell-based immunotherapy compared with interleukin-2 plus interferon-α-2. This body of evidence is limited by the context of the studies (non-U.S.) and choice of a nonstandard comparator. The other 2 RCTs have also reported response rates in favor of CIK therapy with 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 the effects of the technology on health outcomes.

For individuals with gastric cancer who receive CIK cells, the evidence includes 2 meta-analyses encompassing non-randomized trials. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. Both meta-analyses reported statistically significant effects on OS, DFS, and PFS in favor of immunotherapy vs 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 the effects of the technology on health outcomes.

For individuals with colorectal cancer who receive CIK cells, the evidence includes a single RCT and 1 meta-analysis. 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 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 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 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 OS, DSS, QOL, 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 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 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 OS, DSS, QOL, 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-U.S.), 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 the effects of the technology on health outcomes.

Tumor-Infiltrating Lymphocytes

For individuals with melanoma who receive tumor-infiltrating lymphocytes (TIL), the evidence includes a meta-analysis of randomized and non-randomized trials. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The meta-analysis evaluating TIL with interleukin (IL)-2 in patients with cutaneous melanoma reported a objective response rate 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 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 the effects of the technology on health outcomes.

Dendritic Cells

For individuals with glioblastoma multiforme who receive dendritic cells (DC), the evidence includes a systematic review of observational studies. Relevant outcomes are OS, DSS, QOL, 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 1 such RCT have been published but are not informative because the patients were unblinded and results combined for the treatment and placebo arms. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with non-small-cell lung cancer who receive DC, the evidence includes 2 RCTs 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. 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 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 the effects of the technology on health outcomes.

For individuals with medullary thyroid cancer 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 medullary thyroid cancer 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 the effects of the technology on health outcomes.

For individuals with pancreatic cancer who receive DC, the evidence includes a small prospective noncomparative study. Relevant outcomes are OS, DSS, QOL, 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 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 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 OS, DSS, QOL, 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 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 the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Current guidelines from the National Comprehensive Cancer Network[i,ii] do not include recommendations for adoptive immunotherapy to treat cancers of the bladder[44], central nervous system,[45] head and neck,[46] hepatobiliary system,[47] kidney,[48] pancreatic,[49] stomach,[50] thyroid[51], melanoma,[52] or non-small-cell lung cancer.[53]

[i] Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Bladder Cancer V.4.2019, Central Nervous System Cancers V.1.2019, Head and Neck Cancers V.2.2019, Hepatobiliary Cancer V.3.2019, Kidney Cancer V.2.2020, Pancreatic Adenocarcinoma V.3.2019, Gastric Cancer V.2.2019, Thyroid Carcinoma V.1.2019, Cutaneous Melanoma V.2.2019, and Non-Small Cell Lung Cancer V.7.2019. National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed September 2, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org.

[ii] NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

U.S. Preventive Services Task Force Recommendations

Not applicable.

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. 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
2. 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
3. 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
4. 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
5. 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
6. 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
7. 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
8. 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
9. 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
10. 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
11. 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
12. 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
13. 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
14. 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
15. 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
16. 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
17. 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

18. 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
19. 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
20. 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
21. 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
22. 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.
23. 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
24. 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
25. 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
26. 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
27. 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
28. 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
29. 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
30. 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
31. 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
32. 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
33. 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
34. 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
35. 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
36. 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
37. 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
38. Humphries C. Adoptive cell therapy: Honing that killer instinct. Nature. Dec 19 2013; 504(7480): S13-5. PMID 24352359
39. 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
40. 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

41. 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
42. 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
43. 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
44. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: bladder cancer. Version 6.2020. http://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. Accessed September 5, 2020.
45. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: central nervous system cancers. Version 2.2020. http://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed September 6, 2020.
46. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: head and neck cancers. Version 2.2020. http://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed September 9, 2020.
47. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: hepatobiliary cancers. Version 5.2020. http://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. Accessed September 10, 2020.
48. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: kidney cancer. Version 1.2021. https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf. Accessed September 11, 2020.
49. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: pancreatic adenocarcinoma. Version 1.2020. http://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed September 13, 2020.
50. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: gastric cancer. Version 3.2020. http://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf. Accessed September 8, 2020.
51. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: thyroid carcinoma. Version 2.2020. http://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf. Accessed September 14, 2020.
52. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: cutaneous melanoma. Version 3.2020. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf. Accessed September 7, 2020.
53. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: non-small cell lung cancer. Version 6.2020. http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed September 12, 2020.

POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
September 2011	New policy	
March 2013	Replace policy	Policy updated with literature review, 2 systematic reviews added; primary studies added on cytokine-induced killer (CIK) cells; Refs 1, 3- 6, 24 and 27 added, others renumbered and/or removed. Policy statement now includes cytokine-induced killer (CIK) cells, remains investigational.
March 2014	Replace policy	Policy updated with literature search. References 3, 8, 27, and 31 added. No change in policy statements.

Date	Action	Description
March 2015	Replace policy	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.
June 2016	Replace policy	Policy updated with literature review through November 10, 2015; references 13 and 17-18 added. Section on lymphokine-activated killer cell deleted due obsolete intervention. Policy statements unchanged.
December 2017	Replace policy	Policy updated with literature review through April 25, 2017, and FDA documents accessed subsequent to this date; references 3-10, 23-24, 55-58, and 70 were added. Information for tisagenlecleucel and axicabtagene ciloleucel in FEP pharmacy policies noted in related policy section.
March 2019	Replace policy	Policy updated with literature review through October 29, 2018; reference 31 added. Policy statements unchanged.
December 2019	Replace policy	Policy updated with literature review through July 25, 2019; Policy statement wording revised to All applications of adoptive immunotherapy evaluated in this policy are considered investigational.
December 2020	Replace policy	Policy updated with literature review through August 31, 2020; references added. “All adoptive immunotherapy techniques intended to enhance autoimmune effects are considered investigational for the indications included, but not limited to cancers associated with EBV, CMV, nasopharyngeal cancer, renal cell carcinoma, gastric cancer, colorectal cancer, hepatocellular carcinoma, NSCLC, melanoma, glioblastoma multiforme, medullary thyroid cancer, pancreatic cancer, and cancers treated with autologous peripheral T lymphocytes containing tumor antigen-specific T cell receptors." Xpovio added as a related policy.