



FEP Medical Policy Manual

FEP 8.01.01 Adoptive Immunotherapy

Effective Policy Date: January 1, 2020

Original Policy Date: September 2011

Related Policies:

5.21.101 Kymriah

5.21.105 Yescarta

5.90.33 Luxturna

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.

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) and 5.21.105 (Yescarta) 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.

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POLICY STATEMENT

Adoptive immunity in the form of chimeric antigen receptor T-cell therapy (eg, tisagenlecleucel, axicabtagene ciloleucel) for hematologic malignancies is discussed in the FEP policy for each specific FDA product.

All applications of adoptive immunotherapy evaluated in this policy are considered **investigational**.

POLICY GUIDELINES

None

BENEFIT APPLICATION

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

FDA REGULATORY STATUS

On August 30, 2017, tisagenlecleucel (Kymriah™; Novartis) was approved by the Food and Drug Administration for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse.

On May 1, 2018, tisagenlecleucel (Kymriah™; Novartis) was approved by the Food and Drug Administration for the treatment of adults with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy including DLBCL not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

On October 18, 2017, axicabtagene ciloleucel (Yescarta™; Kite Pharma) was approved by the Food and Drug Administration for the treatment of adults with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

These therapies are discussed separately in policies 5.21.101 (Kymriah) and 5.21.105 (Yescarta) 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.

RATIONALE

Summary of Evidence

Cytotoxic T Lymphocytes (CTL)

For individuals with Epstein-Barr-Virus (EBV)-associated cancers who receive CTL, the evidence includes two small, prospective noncomparative cohort studies. The 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.

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For individuals with *Cytomegalovirus*-associated cancers who receive CTL, the evidence includes a single case series. The 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 (CIK)

For individuals with nasopharyngeal carcinoma who receive CIK cells, the evidence includes a single RCT. The relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The RCT reported a numerically favorable but statistically insignificant effect on PFS and OS. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with renal cell carcinoma (RCC) who receive CIK cells, the evidence includes multiple RCTs. The relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The largest of the RCTs reported statistically significant gains in PFS and OS with CIK cell-based immunotherapy compared with IL-2 plus interferon- α -2. This body of evidence is limited by the context of the studies (non-U.S.) and choice of a nonstandard comparator. The other two 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 (GC) who receive CIK cells, the evidence includes a single nonrandomized prospective study and one systematic review and meta-analysis. The relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The prospective cohort study reported statistically significant effects on DFS and OS 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 (CRC) who receive CIK cells, the evidence includes a single RCT and one cohort study. The 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. 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 (HCC) who receive CIK cells, the evidence includes several RCTs. The relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. Several RCTs from Asia have generally reported some benefits in response rates and/or survival. The results of a meta-analysis of these trials have also shown a statistically significant 41% reduction in the hazard of death, but there was considerable heterogeneity across the included studies. This body of evidence is limited by the context of the studies (non-U.S.), small sample sizes, heterogeneous treatment groups, and other methodologic weaknesses. To establish efficacy, the following 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 (NSCLC) who receive CIK cells, the evidence includes multiple RCTs and a systematic review. The 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.

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Tumor-Infiltrating Lymphocytes (TIL)

For individuals with melanoma who receive TIL, the evidence includes a single RCT. The relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. Results of a small RCT have reported no difference in relapse or survival outcomes. Cohort studies in patients with refractory metastatic melanoma have demonstrated response rates of 49% with immunotherapy and 52% to 72% with no immunotherapy. To establish efficacy, the following 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 (DC)

For individuals with glioblastoma multiforme who receive DC, the evidence includes a systematic review of observational studies. The 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 one 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 (NSCLC) who receive DC, the evidence includes two RCTs and a meta-analysis. The 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 (MTC) who receive DC, the evidence includes one prospective noncomparative study. The relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. A small prospective noncomparative study in ten MTC patients treated with ADC 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. The relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The study reported on treatment outcomes for five 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 (TCR), the evidence includes multiple small observational studies. The 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 TCR in melanoma, Hodgkin and non-Hodgkin lymphoma (NHL), 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,⁵⁰ central nervous system,⁵¹ head and neck,⁵² hepatobiliary system,⁵³ kidney,⁵⁴ pancreatic,⁵⁵ stomach,⁵⁶ or thyroid,⁵⁷ melanoma,⁵⁸ or non-small-cell lung cancer.⁵⁹

Footnotes

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.

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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.
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 <i>evaluated in this policy</i> are considered investigational.

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