



MASSACHUSETTS

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Medical Policy

Adoptive Immunotherapy including CAR T-Cell Therapy

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Policy Number: 455

BCBSA Reference Number: 8.01.01

NCD/LCD: N/A

Related Policies

- Cellular Immunotherapy for Prostate Cancer, [#268](#)
- CAR T-Cell Therapy Services for the Treatment of Diffuse Large B-cell Lymphoma (axicabtagene cilleucel or tisagenlecleucel) Prior Authorization Request Form, [#924](#)
- CAR T-Cell Therapy Services for B-cell Acute Lymphoblastic Leukemia (tisagenlecleucel) Prior Authorization Request Form, [#925](#)

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO BlueSM and Medicare PPO BlueSM Members

Prior Authorization Request Form: Adoptive Immunotherapy including CAR T-Cell Therapy Services

This form **must** be completed and faxed to: Medical and Surgical: 1-888-282-0780; Medicare Advantage: 1-800-447-2994.

- [Click here for CAR T-Cell Therapy Services for the Treatment of Diffuse Large B-cell Lymphoma \(axicabtagene cilleucel or tisagenlecleucel\) Prior Authorization Request Form #924](#)
- [Click here for CAR T-Cell Therapy Services for B-cell Acute Lymphoblastic Leukemia \(tisagenlecleucel\) Prior Authorization Request Form #925](#)

Kymriah (tisagenlecleucel) intravenous infusion may be considered **MEDICALLY NECESSARY** for relapsed^a (second or later) or refractory^b patients if they meet **all** of following criteria:

- Confirmed diagnosis of CD19-positive B-cell acute lymphoblastic leukemia with morphologic marrow tumor involvement ($\geq 5\%$ lymphoblasts)
- Are up to 25 years old at the time of infusion
- Have not received prior treatment with tisagenlecleucel or any other gene therapy or are being considered for treatment with any other gene therapy

- Have adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis
- Do not have any of the following:
 - Burkitt lymphoma
 - Active hepatitis B, C, or any uncontrolled infection
 - Grade 2 to 4 graft-versus-host disease
 - Received allogeneic cellular therapy, such as donor lymphocyte infusion, within 6 weeks prior to tisagenlecleucel infusion
 - Patient has active central nervous system 3 acute lymphoblastic leukemia (ie, white blood cell count ≥ 5 cells/ μ L in cerebrospinal fluid with presence of lymphoblasts).*
- The healthcare facility that dispenses and administers Kymriah is enrolled and complies with the Risk Evaluation and Mitigation Strategy known as Kymriah REMS, including:
 - Onsite, immediate access to tocilizumab
 - Availability of a minimum of two doses of tocilizumab for each patient for administration within 2 hours after Kymriah infusion, if needed for treatment of cytokine release syndrome
 - Assurance that healthcare providers who prescribe, dispense or administer Kymriah are trained in the management of cytokine release syndrome and neurologic toxicities.

^a Relapsed disease describes the reappearance of leukemia cells in the bone marrow or peripheral blood after the attainment of a complete remission with chemotherapy and/or allogeneic cell transplant.

^b Refractory (resistant) disease is defined as those patients who fail to obtain complete response with induction therapy, ie, failure to eradicate all detectable leukemia cells (<5% blasts) from the bone marrow and blood with subsequent restoration of normal hematopoiesis (>25% marrow cellularity and normal peripheral blood counts).

*Central nervous system (CNS) disease for B-cell acute lymphoblastic leukemia is defined by the following groups:

- CNS 1: Absence of blasts on cerebrospinal fluid cytospin preparation, regardless of the white blood cell (WBC) count
- CNS 2: WBC count of less than 5/mL and blasts on cytospin findings
- CNS 3: WBC count of 5/mL or more and blasts on cytospin findings and/or clinical signs of CNS leukemia (eg, facial nerve palsy, brain/eye involvement, hypothalamic syndrome).

Yescarta (axicabtagene cilleucel) or Kymriah (tisagenlecleucel) intravenous (except as indicated) infusion may be considered **MEDICALLY NECESSARY** for relapsed or refractory^a patients if they meet **all** of the following criteria:

- Are adults (age ≥ 18) at the time of infusion
- Histologically confirmed diagnosis of diffuse large B-cell lymphoma, not otherwise specified; or primary mediastinal large B-cell lymphoma or high-grade B-cell lymphoma^b or diffuse large B-cell lymphoma arising from follicular lymphoma.
- Received adequate prior therapy including all of the following:
 - Anti-CD20 monoclonal antibody for CD20-positive tumor
 - Anthracycline-containing chemotherapy regimen
 - For subjects with transformed follicular lymphoma, prior chemotherapy for follicular lymphoma and subsequently have chemorefractory disease after transformation to diffuse large B-cell lymphoma
- If patient has a history of allogeneic stem cell transplant, has no signs of active graft versus host disease
- No active autoimmune disease requiring systemic immunosuppression
- Have adequate organ and bone marrow function as determined by the treating oncologist/hematologist
- Have not received prior CD19-directed CAR T-cell therapy treatment or any other gene therapy or are being considered for treatment with any other gene therapy

AND

- Do not have primary central nervous system lymphoma

- The healthcare facility that dispenses and administers Yescarta is enrolled and complies with the Risk Evaluation and Mitigation Strategy including:
 - Onsite, immediate access to tocilizumab, AND
 - Availability of a minimum of two doses of tocilizumab for each patient for administration within 2 hours after Yescarta infusion, if needed for treatment of cytokine release syndrome, AND
 - Assurance that healthcare providers who prescribe, dispense or administer Yescarta are trained in the management of cytokine release syndrome and neurologic toxicities.

^a Relapsed or refractory disease, defined as progression after 2 or more lines of systemic therapy (which may or may not include therapy supported by autologous cell transplant).

^b Tisagenlecleucel intravenous infusion is considered investigational for the treatment of relapsed or refractory primary mediastinal large B-cell lymphoma.

Other adoptive immunotherapy, using adoptive cellular therapy for the administration of cytotoxic T-lymphocytes, cytokine-induced killer cells, tumor-infiltrating lymphocytes, antigen-loaded autologous dendritic cells, or genetically-engineered T-cells is considered **INVESTIGATIONAL**.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization is required .*
Commercial PPO and Indemnity	Prior authorization is required .*
Medicare HMO Blue SM	Prior authorization is required .*
Medicare PPO Blue SM	Prior authorization is required .*

*Prior Authorization Request Form: Adoptive Immunotherapy including CAR T-Cell Therapy Services

This form **must** be completed and faxed to: Medical and Surgical: 1-888-282-0780; Medicare Advantage: 1-800-447-2994.

- [Click here for CAR T-Cell Therapy Services for the Treatment of Diffuse Large B-cell Lymphoma \(axicabtagene cilleucel or tisagenlecleucel\) Prior Authorization Request Form #924](#)
- [Click here for CAR T-Cell Therapy Services for B-cell Acute Lymphoblastic Leukemia \(tisagenlecleucel\) Prior Authorization Request Form #925](#)

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

HCPCS Codes

HCPCS codes:	Code Description
C9399	Unclassified drugs or biologicals
J3490	Unclassified drugs
J3590	Unclassified biologics
J9999	Not otherwise classified, antineoplastic drugs
Q2041	Axicabtagene ciloleucel, up to 200 million autologous anti-cd19 car positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose
Q2042	Tisagenlecleucel, up to 600 million car-positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose
S2107	Adoptive immunotherapy, i.e., development of specific anti-tumor reactivity (e.g., tumor infiltrating lymphocyte therapy) per course of treatment

ICD-10 Procedure Codes

ICD-10-PCS procedure codes:	Code Description
XW033C3	Introduction of Engineered Autologous Chimeric Antigen Receptor T-cell Immunotherapy into Peripheral Vein, Percutaneous Approach, New Technology Group 3
XW043C3	Introduction of Engineered Autologous Chimeric Antigen Receptor T-cell Immunotherapy into Central Vein, Percutaneous Approach, New Technology Group 3

The following CPT codes are considered investigational for **Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:**

CPT Codes

CPT codes:	Code Description
0537T	Chimeric antigen receptor T-cell (CAR-T) therapy; harvesting of blood-derived T lymphocytes for development of genetically modified autologous CAR-T cells, per day
0538T	Chimeric antigen receptor T-cell (CAR-T) therapy; preparation of blood-derived T lymphocytes for transportation (eg, cryopreservation, storage)
0539T	Chimeric antigen receptor T-cell (CAR-T) therapy; receipt and preparation of CAR-T cells for administration
0540T	Chimeric antigen receptor T-cell (CAR-T) therapy; CAR-T cell administration, autologous

Description

Acute Lymphoblastic Leukemia

ALL is a malignancy (clonal) of the bone marrow in which the early lymphoid precursors of the white blood cells (called lymphoblasts) proliferate and replace the normal hematopoietic cells of the marrow. This results in overcrowding of the bone marrow, as well as the peripheral organs (particularly the liver, spleen, and lymph nodes) by the lymphoblasts. As a consequence, the leukemic blasts displace the normal hematopoietic bone marrow and cause cytopenias in all three cell lineages (anemia, thrombocytopenia, granulocytopenia). Leukostasis affecting brain and lung may also occur. Death occurs commonly due to severe pancytopenia and resulting infections. Refractory (resistant) disease is defined as those patients who fail to obtain a complete response with induction therapy, ie, failure to eradicate all detectable leukemia cells (<5% blasts) from the bone marrow and blood with subsequent restoration of normal hematopoiesis (>25% marrow cellularity and normal peripheral blood counts). Relapsed disease

describes the reappearance of leukemia cells in the bone marrow or peripheral blood after the attainment of complete remission. Minimal residual disease (MRD) refers to the presence of disease in cases deemed to be in complete remission by conventional pathologic analysis. MRD positivity is defined as the presence of 0.01% or more ALL cells and has been shown to be a strongest prognostic factor to predict the risk of relapse and death when measured during and after induction therapy in both newly diagnosed and relapsed ALL. In a meta-analysis of 20 studies of 11249 pediatric ALL, Berry et al (2017) reported a hazard ratio for event-free survival in MRD-negative patients compared with MRD-positive patients of 0.23 (95% confidence interval, 0.18 to 0.28).¹

Approximately 5000 cases of B-cell ALL are diagnosed every year in the United States,² and approximately 620 pediatric and young adult patients with B-cell ALL will relapse each year in the United States.³ B-cell ALL is largely a disease of the young, with approximately 60% of cases occurring in patients younger than 20 years old with a median age at diagnosis of 15 years.²

Treatment

While treatable in 85% cases, approximately 15% of children and young adults with ALL will relapse and 2% to 3% of ALL patients are primary refractory.⁴ Retreatment of refractory or relapsed ALL is generally unsuccessful and associated with a high mortality rate.⁵ The 2-year survival rate among patients with ALL who relapse after hematopoietic cell transplantation is 15%.⁶ The Food and Drug Administration (FDA) approved clofarabine (as a single agent or in combination) in 2004 and blinatumomab in 2014 for relapsed and refractory ALL. Reported median objective response rates in the pivotal trials of the 2 agents were 19.7% and 33%, the median durations of response were 2.5 months and 6 months, and median overall survival durations were 3 months and 7.5 months, respectively.^{7,8} Note that the percentages of patients treated with 3 or more prior treatments of clofarabine and blinatumomab trial were 62% and 7%, respectively. Nevertheless, treatment options for patients with relapsed or refractory ALL are limited, associated with poor outcomes and high toxicity and the disease remains incurable.

Diffuse large b-cell lymphoma

DLBCL is the most common histologic subtype of non-Hodgkin lymphoma and accounts for approximately 25% of non-Hodgkin lymphoma cases.⁹ DLBCL exhibits large heterogeneity in morphologic, genetic, and clinical aspects and multiple clinicopathologic entities are defined by the 2016 World Health Organization classification, which are sufficiently distinct to be considered separate diagnostic categories. Teras et al (2016) has estimated that 27650 new cases of DLBCL were diagnosed in the United States in 2016.¹⁰

Treatment

Treatment in the first-line setting (particularly rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) is associated with a 5-year survival rate ranging from 60% to 70%.¹¹ However, based on a number of prognostic factors, 20% to 50% of DLBCL cases are refractory or relapse after first-line chemotherapy.^{12,13} The response to subsequent salvage chemotherapy and consolidation with autologous cell transplantation is suboptimal. A retrospective analysis of the SCHOLAR-1 study by Crump et al (2017), which pooled data from 2, phase 3 clinical trials and 2 observational cohorts, included 636 patients with refractory DLBCL.¹⁴ The objective response rate to the next line of therapy was 26%, with 7% achieving a complete response. Median overall survival was 6.3 months and 2-year survival 20%. Refractory DLBCL was defined as progressive disease or stable disease as best response at any point during chemotherapy (>4 cycles of first-line or 2 cycles of later-line therapy) or as relapse 12 or fewer months after autologous cell transplantation.

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. 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.¹⁵

Cellular Therapy and Dendritic Cell Infusions

The major research challenge in adoptive immunotherapy is to develop immune cells with antitumor reactivity in quantities sufficient for transfer to tumor-bearing patients. In current trials, two 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.”¹⁶ 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 (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 antigens in vivo. ADCs harvested from the patient are either pulsed with antigen or transfected with a viral vector bearing a common cancer antigen. The activated ADCs are then 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 policy # [268](#) 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 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-vs-malignancy effect of donor lymphocytes. In contrast, the adoptive immunotherapy techniques described in this evidence review 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.

Tisagenlecleucel

Tisagenlecleucel is adoptive immunotherapy in which the T-cells of a patient are modified by genetic engineering using a lentiviral vector. The resulting genetic modified cells express a CD-19-directed chimeric antigen receptor protein that consists of an extracellular portion that has a murine anti-CD19 single-chain antibody fragment as well as an intracellular portion that contains T-cell signaling and co-stimulatory domains. Once injected, the genetically modified T-cells selectively target and bind

to CD19 antigen expressed on the surface of B cells and tumors derived from B cells. Subsequently, the intracellular signaling domains play crucial roles in T-cell activation, persistence, and effector functions.¹⁷

Axicabtagene Ciloleucel

Similar to tisagenlecleucel, axicabtagene ciloleucel is adoptive immunotherapy in which the T-cells of a patient are modified genetically using a retroviral vector. The resulting genetically modified cells express a CD-19-directed chimeric antigen receptor protein that has a murine single-chain variable fragment with specificity for CD19. Once injected, the genetically modified T-cells selectively target and bind to CD19 antigen expressed on the surface of normal and malignant B cells.¹⁸

Summary

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.

Cytotoxic T Lymphocytes

For individuals with Epstein-Barr virus-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.

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

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 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. The 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 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 the effects of the technology on health outcomes.

For individuals with gastric cancer 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 disease-free survival 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 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 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 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.

Tumor-Infiltrating Lymphocytes

For individuals with melanoma who receive tumor-infiltrating lymphocytes, 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

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 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 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 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. 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, 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 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.

Tisagenlecleucel

For individuals who are up to 25 years of age with relapsed or refractory B-cell acute lymphoblastic leukemia who receive tisagenlecleucel, the evidence includes multiple single-arm prospective trials. The relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The pivotal single-arm trials reported an 83% response rate (measured by complete response or complete remission with incomplete blood count) in heavily pretreated patients. All patients who achieved complete remission or complete remission with incomplete blood count were also minimal residual disease-negative, which is predictive of survival in acute lymphoblastic leukemia patients. After a median follow-up of 4.8 months, the median duration of response was not reached. The observed benefits seen with tisagenlecleucel were

offset by a high frequency and severity of adverse events. Cytokine release syndrome was observed in more than half (63%) of the patients, and approximately 40% had an adverse event at grade 4 or higher. Long-term follow-up and real-world evidence are required to assess the generalizability of tisagenlecleucel efficacy and safety outside of the clinical trial setting. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are adults with a histologically confirmed diagnosis of aggressive non-Hodgkin lymphoma (eg, diffuse large B-cell lymphoma not otherwise specified, high-grade B-cell lymphoma, transformed follicular lymphoma) who receive tisagenlecleucel, the evidence includes a single-arm prospective trial. The relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The pivotal single-arm trial reported a 50% overall response rate (measured by complete or partial remission) in heavily pretreated patients. After a median follow-up of 9.4 months, the median duration of response was not reached. The observed benefits were offset by a high frequency and severity of adverse events. Any grade cytokine release syndrome was observed in 74% of the patients, and 23% had grade 3 or higher cytokine release syndrome. Long-term follow-up and real-world evidence are required to assess the generalizability of tisagenlecleucel efficacy and safety outside of the clinical trial setting. The manufacturer has agreed to a postmarketing requirement observational registry study to collect safety information for patients treated with the marketed product. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Axicabtagene Ciloleucel

For individuals who are adults with a histologically confirmed diagnosis of aggressive non-Hodgkin lymphoma (eg, diffuse large B-cell lymphoma not otherwise specified, high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, transformed follicular lymphoma) who receive axicabtagene ciloleucel, the evidence includes a single-arm prospective trial. The relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The pivotal single-arm trial reported a 72% overall response rate (measured by complete or partial remission) in heavily pretreated patients. After a median follow-up of 7.9 months, the median duration of response was 9.2 months. The observed benefits were offset by a high frequency and severity of adverse events. Cytokine release syndrome was observed in more than half (63%) of the patients, and 44% had an adverse event at grade 3 or higher. Long-term follow-up and real-world evidence are required to assess the generalizability of axicabtagene ciloleucel efficacy and safety outside of the clinical trial setting. The manufacturer has agreed to a postmarketing requirement observational registry study to collect safety information for patients treated with the marketed product. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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.

Policy History

Date	Action
3/2019	BCBSA National medical policy review. Description, summary and references updated. Policy statements unchanged.
1/2019	Clarified coding information.
8/2018	BCBSA National medical policy review. Tisagenlecleucel added to the second medically necessary policy statement with modified criteria. Effective 8/1/2018.
6/2018	BCBSA National medical policy review. Policy statement clarified, changing “2 or 3” to “3”, to read: “Patient has active central nervous system 3 acute lymphoblastic leukemia (ie, white blood cell count \geq 5 cells/ μ L in cerebrospinal fluid with presence of lymphoblasts).” Prior Authorization Information reformatted.
4/2018	Clarified coding information.
2/2018	BCBSA National medical policy review. Policy criteria for Kymriah and Yescarta clarified.

1/2018	Clarified coding information. Preauthorization request form for Yescarta and Kymriah added.
11/2017	Medical policy criteria for Yescarta clarified. Effective 11/17/17.
11/2017	BCBSA National medical policy review. New medically necessary indications added for Kymriah (tisagenlecleucel). Effective 11/7/2017. New medically necessary indications added for Yescarta (axicabtagene cilleucel). Effective 11/7/2017. Clarified coding information.
5/2016	BCBSA National medical policy review. Section on lymphokine-activated killer cell deleted due to obsolete intervention. Effective 5/1/2016.
5/2015	BCBSA National medical policy review. Clarified coding information. New investigational indications described. Effective 5/1/2015.
3/2014	New references added from BCBSA National medical policy.
6/2013	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. Effective 6/1/2013.
11/2011-4/2012	Medical policy ICD 10 remediation: Formatting, editing and coding updates. No changes to policy statements.
1/17/2012	BCBSA National medical policy review. No changes to policy statements.
1/1/2012	Updated removing information on donor leukocyte infusion which is now addressed in medical policy #338.
7/2011	Reviewed - Medical Policy Group - Hematology and Oncology. No changes to policy statements.
9/2010	Reviewed - Medical Policy Group - Hematology and Oncology. No changes to policy statements.
4/2010	BCBSA National medical policy review. No changes to policy statements.
9/2009	Reviewed - Medical Policy Group - Hematology and Oncology. No changes to policy statements.
9/2009	BCBSA National medical policy review. Changes to policy statements.
2/2009	BCBSA National medical policy review. No changes to policy statements.
10/2008	Reviewed - Medical Policy Group - Hematology and Oncology. No changes to policy statements.
9/2008	BCBSA National medical policy review. No changes to policy statements
11/2007	BCBSA National medical policy review. No changes to policy statements.
9/2007	Reviewed - Medical Policy Group - Hematology and Oncology. No changes to policy statements.
8/2007	BCBSA National medical policy review. No changes to policy statements.
3/2007	Reviewed - Medical Policy Group- Allergy and ENT/Otolaryngology. No changes to policy statements.

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