MASSACHUSETTS

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Medical Policy

Chimeric Antigen Receptor Therapy for Leukemia and Lymphoma

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Policy Number: 066

BCBSA Reference Number: 8.01.63 (For Plan internal use only)

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Policy

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Tisagenlecleucel (Kymriah): B-cell Acute Lymphoblastic Leukemia

Tisagenlecleucel may be considered **MEDICALLY NECESSARY** for relapsed[a] (second or later) or refractory[b] patients if they meet **ALL** of following **criteria 1 through 5**:

1. Confirmed diagnosis of CD19-positive B-cell acute lymphoblastic leukemia with morphologic marrow tumor involvement (≥ 5% lymphoblasts)
2. Are up to 25 years old at the time of infusion
3. Have not received prior FDA approved, CD19-directed, chimeric antigen receptor T therapy
4. Have adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis

5. 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
   - Concomitant genetic syndrome with the exception of Down syndrome
   - 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/µL in cerebrospinal fluid with presence of lymphoblasts).* **AND**
6. 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).

Tisagenlecleucel (Kymriah): Non-Hodgkin Lymphoma

Tisagenlecleucel may be considered **MEDICALLY NECESSARY** for relapsed[c] or refractory[c] patients with aggressive types of non-Hodgkin lymphoma if they meet **criteria 1 through 6**:
1. Are adults (age ≥18) at the time of infusion
2. Histologically confirmed diagnosis of diffuse large B-cell lymphoma, not otherwise specified; high-grade B-cell lymphoma **or** diffuse large B-cell lymphoma arising from follicular lymphoma.
3. 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
4. Have adequate organ and bone marrow function as determined by the treating oncologist/hematologist
5. Have not received prior FDA approved, CD19-directed, chimeric antigen receptor T therapy
6. Do not have primary central nervous system lymphoma, **AND**
7. The healthcare facility that dispenses and administers Kymriah 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 Kymriah infusion, if needed for treatment of cytokine release syndrome, **AND**
- Assurance that healthcare providers who prescribe, dispense or administer Kymriah are trained in the management of cytokine release syndrome and neurologic toxicities.

[c]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).

Tisagenlecleucel is considered **INVESTIGATIONAL** for the treatment of relapsed or refractory primary mediastinal large B-cell lymphoma.

Axicabtagene ciloleucel (Yescarta): Non-Hodgkin Lymphoma

Axicabtagene ciloleucel infusion is considered **MEDICALLY NECESSARY** for relapsed or refractory[c] patients with aggressive types of non-Hodgkin lymphoma if they meet **criteria 1 through 6**:

1. Are adults (age ≥18) at the time of infusion
2. 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 **or** diffuse large B-cell lymphoma arising from follicular lymphoma.
3. 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
4. Have adequate organ and bone marrow function as determined by the treating oncologist/hematologist
5. Have not received prior FDA approved, CD19-directed, chimeric antigen receptor T therapy, **AND**
6. Do not have primary central nervous system lymphoma, **AND**
7. The healthcare facility that dispenses and administers Yescarta is enrolled and complies with the Risk Evaluation and Mitigation Strategy including:
    a. Onsite, immediate access to tocilizumab, **AND**
    b. 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**
    c. Assurance that healthcare providers who prescribe, dispense or administer Yescarta are trained in the management of cytokine release syndrome and neurologic toxicities.

[c] Relapsed or refractory disease is defined as progression after 2 or more lines of systemic therapy (which may or may not include therapy supported by autologous cell transplant).

Axicabtagene Ciloleucel (Yescarta): Follicular Lymphoma

Axicabtagene ciloleucel is considered **MEDICALLY NECESSARY** for relapsed or refractory[c] patients with follicular lymphoma if they meet **criteria 1 through 6**:

1. Are adults (age ≥18) at the time of infusion, **AND**
2. Histologically confirmed diagnosis of follicular lymphoma, **AND**
3. Received two or more lines of systemic therapy for treatment of follicular lymphoma, **AND**
4. Have adequate organ and bone marrow function as determined by the treating oncologist/hematologist, **AND**
5. Have not received prior FDA approved, CD19-directed, chimeric antigen receptor T therapy, **AND**
6. Do not have primary central nervous system lymphoma, **AND**
7. 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.

[c] Relapsed or refractory disease is defined as progression after 2 or more lines of systemic therapy (which may or may not include therapy supported by autologous cell transplant)

Brexucabtagene Autoleucel (Tecartus): Mantle Cell Lymphoma

Brexucabtagene autoleucel is considered **MEDICALLY NECESSARY** for relapsed or refractory mantle cell lymphoma[d] if they meet **criteria 1 through 5**:

1. Are adults (age ≥18) at the time of infusion, **AND**
2. Histologically confirmed diagnosis of mantle cell lymphoma, **AND**
3. Received adequate prior therapy including chemotherapy and an anti-CD20 antibody, **OR** a Bruton tyrosine kinase inhibitor (example ibrutinib or acalabrutinib), **AND**
4. Have adequate organ and bone marrow function as determined by the treating oncologist/hematologist, **AND**
5. Have not received prior FDA approved, CD19-directed, chimeric antigen receptor T therapy, **AND**
6. The healthcare facility that dispenses and administers Tecartus is enrolled and complies with the Risk Evaluation and Mitigation Strategy including:
    a. Onsite, immediate access to tocilizumab, **AND**
    b. Availability of a minimum of two doses of tocilizumab for each patient for administration within 2 hours after Tecartus infusion, if needed for treatment of cytokine release syndrome, **AND**

    Assurance that healthcare providers who prescribe, dispense or administer Tecartus are trained in the management of cytokine release syndrome and neurologic toxicities.

[d] Relapsed or refractory disease is defined as disease progression after last regimen or failure to achieve a partial remission or complete remission to the last regimen

Brexucabtagene Autoleucel (Tecartus): B-cell Acute Lymphoblastic Leukemia

Brexucabtagene autoleucel is considered **MEDICALLY NECESSARY** for relapsed[a] or refractory[b] patients with B-cell acute lymphoblastic leukemia if they meet **criteria 1 through 5**:

1. Confirmed diagnosis of CD19-positive B-cell acute lymphoblastic leukemia with morphologic bone marrow tumor involvement (≥5% lymphoblasts), **AND**
2. Are 18 years or older at the time of infusion, **AND**
3. Have adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis, **AND**
4. Have not received prior FDA approved, CD19-directed, chimeric antigen receptor T therapy, **AND**
5. 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
    - Concomitant genetic syndrome associated with bone marrow failure with the exception of Down syndrome
    - Received allogeneic cellular therapy, such as donor lymphocyte infusion, within 6 weeks prior to brexucabtagene autoleucel infusion
    - Active central nervous system acute lymphoblastic leukemia (ie, white blood cell count ≥5 cells/μL in cerebrospinal fluid with presence of lymphoblasts), **AND,**
6. The healthcare facility that dispenses and administers Tecartus 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 Tecartus infusion, if needed for treatment of cytokine release syndrome, **AND**
- Assurance that healthcare providers who prescribe, dispense or administer Tecartus 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).

Lisocabtagene Maraleucel (Breyanzi): Non-Hodgkin Lymphoma

Lisocabtagene maraleucel is considered **MEDICALLY NECESSARY** for relapsed or refractory[c] patients with aggressive types of non-Hodgkin lymphoma if they meet **criteria 1 through 6**:

1. Are adults (age ≥18) at the time of infusion
2. Histologically confirmed diagnosis of diffuse large B-cell lymphoma not otherwise specified (including diffuse large B-cell lymphoma arising from indolent lymphoma); high-grade B-cell lymphoma or primary mediastinal large B-cell lymphoma or follicular lymphoma grade 3B
3. 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 chemo-refractory disease after transformation to diffuse large B-cell lymphoma
4. Have adequate organ and bone marrow function as determined by the treating oncologist/hematologist
5. Have not received prior FDA approved, CD19-directed, chimeric antigen receptor T therapy, **AND**
6. Do not have primary central nervous system lymphoma,
7. The healthcare facility that dispenses and administers Breyanzi 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 Breyanzi infusion, if needed for treatment of cytokine release syndrome, **AND**
   - Assurance that healthcare providers who prescribe, dispense or administer Breyanzi are trained in the management of cytokine release syndrome and neurologic toxicities.

[c] Relapsed or refractory disease is defined as progression after 2 or more lines of systemic therapy (which may or may not include therapy supported by autologous cell transplant).

Tisagenlecleucel, axicabtagene ciloleucel, brexucabtagene autoleucel, and lisocabtagene maraleucel are considered **INVESTIGATIONAL** when the above criteria are not met.

Tisagenlecleucel, axicabtagene ciloleucel, brexucabtagene autoleucel, and lisocabtagene maraleucel are considered **INVESTIGATIONAL** for all other indications.

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**.

Requesting Prior Authorization Using Authorization Manager
Providers will need to use Authorization Manager to submit initial authorization requests for services. Authorization Manager, available 24/7, is the quickest way to review authorization requirements, request authorizations, submit clinical documentation, check existing case status, and view/print the decision letter. For commercial members, the requests must meet medical policy guidelines.

To ensure the request is processed accurately and quickly:
- Enter the facility's NPI or provider ID for where services are being performed.
- Enter the appropriate surgeon's NPI or provider ID as the servicing provider, *not* the billing group.

Authorization Manager Resources
- Refer to our Authorization Manager page for tips, guides, and video demonstrations.

Complete Prior Authorization Request Form using Authorization Manager
- CAR T-Cell Therapy Services for Treatment of Diffuse Large B-cell Lymphoma (924)
- CAR T-Cell Therapy Services for B-cell Acute Lymphoblastic Leukemia (tisagenlecleucel) (925)
- CAR T-Cell Therapy Services for Mantle Cell Lymphoma (Brexucabtagene Autoleucel) (940)
- CAR T-Cell Therapy Services for Non-Hodgkin Lymphoma (Lisocabtagene Maraleucel) (941)
- CAR T-Cell Therapy Services for Follicular Lymphoma (Axicabtagene Ciloleucel) (944)
- CAR T-Cell Therapy Services for B-cell Acute Lymphoblastic Leukemia (Brexucabtagene Autoleucel) Prior Authorization Request Form (945)

For out of network providers: Requests should still be faxed to 888-973-0726.

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
Q2053	Brexucabtagene autoleucel, up to 200 million autologous anti-cd19 car positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose
Q2054	Lisocabtagene maraleucel, up to 110 million autologous anti-cd19 car-positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose

ICD-10 Procedure Codes

ICD-10-PCS procedure codes:	Code Description
XW033H7	Introduction of Axicabtagene Ciloleucel Immunotherapy into Peripheral Vein, Percutaneous Approach, New Technology Group 7
XW043H7	Introduction of Axicabtagene Ciloleucel Immunotherapy into Central Vein, Percutaneous Approach, New Technology Group 7
XW033J7	Introduction of Tisagenlecleucel Immunotherapy into Peripheral Vein, Percutaneous Approach, New Technology Group 7
XW043J7	Introduction of Tisagenlecleucel Immunotherapy into Central Vein, Percutaneous Approach, New Technology Group 7
XW033M7	Introduction of Brexucabtagene Autoleucel Immunotherapy into Peripheral Vein, Percutaneous Approach, New Technology Group 7
XW043M7	Introduction of Brexucabtagene Autoleucel Immunotherapy into Central Vein, Percutaneous Approach, New Technology Group 7
XW033N7	Introduction of Lisocabtagene Maraleucel Immunotherapy into Peripheral Vein, Percutaneous Approach, New Technology Group 7
XW043N7	Introduction of Lisocabtagene Maraleucel Immunotherapy into Central Vein, Percutaneous Approach, New Technology Group 7

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

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)

B-cell 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 3 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. Minimal residual disease positivity is defined as the presence of 0.01% or more ALL cells and has been shown to be the 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 11,249 pediatric ALL patients, 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 5,000 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.[3,] B-cell ALL is largely a disease of the young, with approximately 60% of cases occurring in patients younger than 20 years, with a median age at diagnosis of 15 years.[2,]

Treatment
While treatable in 85% of 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 U.S. Food and Drug Administration (FDA) approved clofarabine (as a single agent or in combination therapy) 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 (OS) 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
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,] Diffuse large B cell lymphoma 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. The incidence of DLBCL is approximately 7 cases per 100,000 persons per year. [10,]

Treatment
Treatment in the first-line setting includes multiple chemotherapy and/or immunotherapy options that typically involve rituximab. While the majority of patients respond well to first-line immunochemotherapy combinations containing rituximab, 10 to 15% have primary refractory disease within 3 months after treatment initiation and another 20 to 35% have a relapse.[11,] Of those who relapse or are refractory, 40 to 60% of patients may respond to second-line chemotherapy. Treatment of relapsed/refractory cases is generally stratified according to hematopoietic cell transplant eligibility. There is general consensus that salvage therapy followed by autologous transplantation is the preferred treatment for medically eligible patients with a first relapse of DLBCL or primary refractory DLBCL. Approximately 50% of patients who relapse or are refractory to first line agents proceed to autologous hematopoietic stem-cell transplantation, and of these, approximately 30 to 40% remain progression-free 3 years after transplantation.[12,13,14,15,16,]For patients who are ineligible for second-line therapy that includes high-dose chemotherapy and hematopoietic stem-cell transplantation, prognosis is often poor with a median OS of 4.4 months. Overall survival at 1 year is 23% and 16% at year 2.[16,] For patients who relapse after

autologous transplantation, options are limited and include allogeneic hematopoietic stem-cell transplantation. However, the procedure can only be performed if the patient is chemo-responsive and a donor is available. Further, the procedure is associated with a high risk of complications. The mortality risk unrelated to disease relapse is 23% at 1 year.[17,18,19,] The Food and Drug Administration (FDA) has also approved agents for refractory/relapsed DLBCL including pembrolizumab (Keytruda), polutuzumab vedotin-piiq (Polivy), selinexor (Xpovio), and tafasitamab-cxix (Monjuvi).

Mantle Cell Lymphoma
Mantle cell lymphoma (MCL) is a rare B-cell malignancy classified as an aggressive form of non-Hodgkin lymphoma that arises from cells originating in the "mantle zone" of the lymph node and typically affects men over the age of 60. It accounts for approximately 3-6% of all non-Hodgkin lymphoma in the United States and differs from DLBCL (another subtype of non-Hodgkin lymphoma).[20,21,22,] In 2018, the overall incidence of MCL in the U.S was 3,500 with a 5-year and 10-year prevalence of 12,000 and 18,000 cases. The median age at the time of diagnosis is 68, a majority of patients are non-Hispanic white males and more than 70% of patients present with stage IV disease.[23,24,] The majority (75%) of cases initially present with lymphadenopathy while presentation is extranodal in the remaining 25 percent. In most cases of MCL, chromosomal translocation results in aberrant expression of cyclin D1, leading to cell cycle dysregulation.[25,] Many signaling pathways are constitutively activated and/or deregulated in MCL, including the B-cell receptor signaling pathway.[26,]

Treatment
There is no standard of care that exists for second-line and higher chemotherapy when a patient has relapsed or refractory MCL.[27,] Second line therapies typically depend on the front line therapy utilized, comorbidities, the tumor's sensitivity to chemotherapy, and overall risk-benefit. Potential salvage regimens include ibrutinib, acalabrutinib, lenalidomide, combination chemotherapy, bortezomib, and temsirolimus.

Despite the availability of multiple treatments, MCL is not curable (with the possible exception of hematopoietic cell transplantation). Median OS in modern trials incorporating intensive therapy is 8 to 10 years with no plateau in the survival curve. Shorter survival times are seen with less intensive therapy. Multiple prognostic indices are used in MCL patients to guide course of treatment. First-line treatment of MCL can consist of aggressive or less-aggressive therapy, depending on patient status at baseline.[26,] It generally consists of chemotherapy in combination with rituximab. Only 30 to 40% of patients have a durable long term remission after first line chemo immunotherapy.[28,] Progression is common, with a median time to treatment failure of less than 18 months. Virtually all patients will have refractory or recurrent disease. Treatment of recurrent MCL is difficult, due to the rapid development of chemotherapy resistance. There are multiple preferred chemotherapy regimens that may be offered and choice is primarily made based on prior treatment history, patient comorbidities, and performance status. The expected toxicities of a given regimen as well as clinician's experience with the regimens are additional considerations. A preferred order for their use has not been established. Most of these regimens have not been compared directly in randomized trials. Given the limited efficacy of these agents and the paucity of data comparing these various treatment options, participation in a clinical trial is encouraged whenever possible. Complete response rates in previously treated or relapsed MCL are generally low (<30%) and have limited response durations. Among patients who have disease progression after the receipt of Bruton's kinase inhibitor (BTK) therapy, the reported objective response rate ranges from 25 to 42% with a median OS of 6 to 10 months with salvage therapies.[29,30,31,32,] Allogeneic stem-cell transplantation may be an option for selected patients. However, non–relapse-related mortality remains high at 10 to 24%.[33,] While the clinical course of MCL is generally aggressive, a small proportion of patients with low stage and low-risk disease may have an indolent course, managed by observation, splenectomy, or treatment with alkylating agents analogous to the treatment of patients with small lymphocytic lymphoma or follicular lymphoma.

Follicular lymphoma
Follicular lymphoma is the second most common subtype of non-Hodgkin lymphomas and is associated with an excellent prognosis for most patients with a median OS >20 years.[34,] Approximately 40 to 80% of patients treated respond to initial chemoimmunotherapy while 10% do not respond (ie, refractory

disease). However, conventional therapy for follicular lymphoma is not curative and most of these patients ultimately develop progressive disease.[35.] The prevalence of follicular lymphoma in the United States is approximately 2.7 per 100,000 individuals per year. The 5-year survival rate may be as high as 89.7% and the median age at diagnosis is 63 years old.[36.]

Patients with advanced-stage follicular lymphoma after ≥2 lines of therapy reported a complete response rate with approved therapies ≤14%, and median duration of response (DOR) ≤13 months.[37,38,39.]

Treatment
Initial treatment depends on the stage of disease at presentation. The first and second line treatments for Grade 1-2 follicular lymphoma include excision, radiation therapy, and a systemic therapy with a combination or a single use of an alkylating agent (e.g., bendamustine, cyclophosphamide, and chlorambucil), an anti-CD20 monoclonal antibody (e.g, rituximab, obinutuzumab, and ibritumomab), and an immunomodulatory agent (e.g., lenalidomide).[40.] Other systemic agents, such as vinca alkaloid (e.g., vincristine), anthracycline (e.g., doxorubicin), and a corticosteroid (e.g., prednisone) are also often included in the treatment regimens. Allogeneic hematopoietic cell transplant is used selectively.

There is no standard therapy for patients with relapsed or refractory follicular lymphoma and practice varies widely. Patients with late relapse are treated with an anti-CD20 monoclonal antibody (rituximab or obinutuzumab) either alone or in combination with chemotherapy or lenalidomide. The choice between immunotherapy alone versus combination therapy in late relapse depends largely on patient performance status. Novel FDA approved agents for treatment in the multiple relapse/refractory setting include phosphoinositide 3-kinase (PI3K) inhibitors (copanlisib, duvelisib, idelalisib, umbralisib), lenalidomide, tazemetostat, and radioimmunotherapy. The choice is primarily made based on the patient's prior treatment, the expected toxicity profile of the selected regimen, route of administration, and clinician experience with the regimens.[40.]

Commercial Chimeric Antigen Receptor T-Cell Therapies Available in the United States
As of March 2021, there are 4 CAR T-cell therapies approved by the FDA for the treatment of cancer. All 4 are CD19-targeting CAR T-cell immunotherapies in which a patient's own T-cells are genetically engineered using a viral vector to express a synthetic receptor called the chimeric antigen receptor. 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. Tisagenlecleucel and brexucabtagene autoleucel are approved for treatment of subsets of patients with leukemia and lymphoma and axicabtagene ciloleucel and lisocabtagene maraleucel are approved to treat subsets of patients with lymphoma.

Summary

Description
Chimeric antigen receptor (CAR) T-cells are genetically engineered cells that represent a novel class of cancer immunotherapy. In general, the process of autologous CAR T-cell therapy begins with harvesting white blood cells from the patient via leukapheresis followed by T-cell receptor activation and genetic engineering via retroviral or lentiviral transduction. After the CAR T-cells are generated, they are expanded to clinically relevant numbers, undergo quality control testing, and are cryopreserved. Commercial CAR T-cell products are manufactured at a centralized facility, necessitating transfer of the apheresis product to the manufacturing site, and the final cryopreserved CAR T-cell product back to the treatment facility. Typically, the patient undergoes lymphodepleting chemotherapy to create a favorable immune environment for CAR T-cell activity prior to receiving a single intravenous infusion of the product. Four commercial CAR T-cell products have been approved by the U.S. Food and Drug Administration for the treatment of lymphoma and leukemia. Tisagenlecleucel and brexucabtagene autoleucel are approved for treatment of subsets of patients with leukemia and lymphoma and axicabtagene ciloleucel and lisocabtagene maraleucel are approved to treat subsets of patients with lymphoma.

Summary of Evidence
Tisagenlecleucel
For individuals who are up to 25 years of age with relapsed or refractory B-cell acute lymphoblastic leukemia (ALL) who receive tisagenlecleucel, the evidence includes a single-arm prospective trial.

Relevant outcomes are overall survival (OS), disease-specific survival (DSS), quality of life (QOL), and treatment-related mortality and morbidity. The pivotal single-arm trial reported a 81% response rate (measured by complete response (CR) or complete remission with incomplete blood count) in heavily pretreated patients. All patients who achieved CR or complete remission with incomplete blood count were also minimal residual disease (MRD)-negative, which is predictive of survival in ALL patients. After a median follow-up of 13.1 months, the median duration of response (DOR) was not reached. The observed benefits seen with tisagenlecleucel were offset by a high frequency and severity of adverse events. Cytokine release syndrome (CRS) was observed in more than half (77%) of patients, and approximately 88% had an adverse event at grade 3 or higher. Long-term follow-up, real-world evidence, and post-marketing studies 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 an improvement in the net health outcome.

For individuals who are adults with a histologically confirmed diagnosis of aggressive non-Hodgkin lymphoma (NHL) (eg, diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma, transformed follicular lymphoma) who receive tisagenlecleucel, the evidence includes a single-arm prospective trial. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The pivotal single-arm trial reported a 52% overall response rate (ORR; measured by complete or partial responses) in heavily pretreated patients. After a median follow-up of 14 months, the median DOR was not reached. The observed benefits were offset by a high frequency and severity of adverse events. Any grade CRS was observed in 58% of the patients, and 63% had an adverse event suspected to be related to study drug at grade 3 or higher. Long-term follow-up, real-world evidence, and post-marketing studies 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 an improvement in the net health outcome.

Axicabtagene Ciloleucel
For individuals who are adults with a histologically confirmed diagnosis of aggressive NHL (eg, DLBCL 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. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The pivotal single-arm trial reported a 83% ORR (measured by complete or partial remission) in heavily pretreated patients. After a median follow-up of 27.1 months, the median DOR was 11.1 months. The observed benefits were offset by a high frequency and severity of adverse events. Cytokine release syndrome was observed in more than half of patients, and 98% 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 evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are adults with a histologically confirmed diagnosis of relapsed or refractory follicular lymphoma, the evidence includes a single-arm prospective trial. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The ZUMA-5 study enrolled adult patients with relapsed refractory follicular lymphoma after 2 or more lines of systemic therapy including the combination of an anti-CD20 monoclonal antibody and an alkylating agent. Of 120 patients who received axicabtagene ciloleucel, interim data for 81 consecutive patients who completed at least 9 months of follow-up from date of first response was reported with a median follow-up of 14.5 months. The primary efficacy analysis demonstrated an ORR of 91% with a 60% rate of CR. The median DOR was not reached. At 12 months, 76% remained in remission. 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 evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Brexucabtagene Autoleucel
For individuals who are adults with relapsed or refractory mantle cell lymphoma (MCL) who receive brexucabtagene autoleucel, the evidence includes 1 phase II single-arm study. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The study enrolled adult

patients with relapsed refractory MCL who were heavily pre-treated. Of 74 patients enrolled, therapy was successfully manufactured for 71 (96%) and administered to 68 (92%). Results were reported for 60 pre-specified evaluable patients with a median follow-up (as of the July 24, 2019 data cutoff date) of 12.3 months (range, 7.0 to 32.3). The primary efficacy analysis demonstrated an ORR of 87% with a 62% rate of CR. The median DOR, progression-free survival (PFS), and median OS were not reached. Fifty-seven percent of patients remained in remission at data cutoff, and the estimated 12-month PFS and OS rates were 61% and 83%, respectively. Among patients who have disease progression after Bruton's kinase inhibitor therapy, the reported ORR ranges from 25 to 42% with a median OS of 6 to 10 months with salvage therapies. In the absence of a randomized controlled trial (RCT), it is difficult to draw comparisons with currently available salvage treatment. No notable study limitations were identified. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are adults with relapsed or refractory B-cell ALL who receive brexucabtagene autoleucel, the evidence includes a single-arm prospective trial. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The pivotal single-arm trial reported a 52% response rate (measured by CR or complete remission with incomplete blood count) in heavily pretreated patients. A majority of patients who achieved a CR or complete remission with incomplete blood count were also MRD negative, which is predictive of survival in ALL patients. After a median follow-up of 7.1 months for responders, the median DOR was not reached. The observed benefits seen with brexucabtagene autoleucel must be balanced with consideration of a high frequency and severity of adverse events. Cytokine release syndrome and neurotoxicity are known "class adverse effects" of CAR T-cell therapies with an immunologic basis. Cytokine release syndrome was observed in more than half (89%) of the patients and approximately 24% had an adverse event at grade 3 or higher. Long-term follow-up, real-world evidence, and post-marketing studies are required to further assess the generalizability of brexucabtagene autoleucel efficacy and safety outside of a clinical trial setting. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Lisocabtagene Maraleucel
For individuals who are adults with relapsed or refractory DLBCL not otherwise specified (including DLBCL arising from indolent lymphoma); high-grade B-cell lymphoma or primary mediastinal large B-cell lymphoma or follicular lymphoma grade 3B who receive lisocabtagene maraleucel, the evidence includes a single-arm prospective trial. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. In 299 patients who underwent leukapheresis, therapy was successfully administered to 255 (85%). Of these, 192 were evaluable for efficacy. Twelve were not evaluable due to absence of positron emission tomography (PET) positive disease at study baseline or after bridging therapy and 51 (17%) either received CAR T-cells outside of the intended dose range (n=26) or received CAR T-cells that did not meet product specifications (manufacturing failures; n=25). The primary efficacy analysis demonstrated an ORR of 73% with a 55% rate of CR. The median DOR was 16.7 months. Response durations were longer in patients who achieved a CR, as compared to patients with a best response of a partial response. Of the 104 patients who achieved a CR, 68 (65%) had remission lasting at least 6 months and 64 (62%) had remission lasting at least 9 months. Cytokine release syndrome, including fatal or life-threatening reactions, occurred in 46% of patients, including ≥ Grade 3 disease in 4% of patients. The median duration of CRS was 5 days (range 1 to 30 days) in all patients, including those who died or had the syndrome ongoing at time of death. No notable study limitations were identified. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Policy History

Date	Action
3/2024	Clarified coding information
9/2023	Policy clarified to include prior authorization requests using Authorization Manager.
1/2022	Annual policy review. New medically necessary indications described for B-cell acute lymphoblastic leukemia. Brexucabtagene autoleucel is considered medically necessary for adult patients with relapsed/refractory B-cell acute lymphoblastic leukemia. Effective 1/1/2022.

10/2021	Clarified coding information.
7/2021	Annual policy review. New medically necessary and investigational indications described for Axicabtagene ciloleucel for adult patients with elapsed or refractory follicular lymphoma after 2 or more lines of systemic therapy. Effective 7/1/2021. Policy criteria clarified to state: Patients have not received prior FDA approved, CD19-directed, chimeric antigen receptor T therapy. Clarified coding information.
5/2021	Annual policy review. New medically necessary indications described. Lisocabtagene maraleucel is considered medically necessary for adult patients with specific types of aggressive non-Hodgkin lymphoma. The title of the policy was changed from Chimeric Antigen Receptor Therapy for Hematologic Malignancies to Chimeric Antigen Receptor Therapy for Leukemia and Lymphoma. Effective 5/1/2021.
4/2021	Medicare information removed. See MP #132 Medicare Advantage Management for local coverage determination and national coverage determination reference.
4/2021	Clarified coding information.
1/2021	Clarified coding information.
12/2020	Annual policy review. New medically necessary indications described for brexucabtagene autoleucel for mantle cell lymphoma. Clarified coding information. Effective 12/1/2020.
12/2019	New policy created from policy #455 Adoptive Immunotherapy. FDA-approved tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta) therapies were moved from policy #455 to create a new standalone policy #066 Chimeric Antigen Receptor Therapy for Hematologic Malignancies. Policy statements unchanged.
3/2019	Annual policy review. Description, summary and references updated. Policy statements unchanged.
1/2019	Clarified coding information.
8/2018	Annual policy review. Tisagenlecleucel added to the second medically necessary policy statement with modified criteria. Effective 8/1/2018.
6/2018	Annual 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 ≥5 cells/µL in cerebrospinal fluid with presence of lymphoblasts).” Prior Authorization Information reformatted.
4/2018	Clarified coding information.
2/2018	Annual policy review. Policy criteria for Kymriah and Yestcarta clarified.
1/2018	Clarified coding information. Preauthorization request form for Yescarta and Kymriah added.
11/2017	Medical policy criteria for Yescarta clarified. Effective 11/17/2017.
11/2017	Annual 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.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

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Repeat Infusions

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