LifeWise
Health Plan of Washington

# MEDICAL POLICY – 8.01.63

# Chimeric Antigen Receptor Therapy for Leukemia and Lymphoma

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| BCBSA Ref. Policy: | 8.01.63 | |
| Effective Date: | July 1, 2024 | RELATED MEDICAL POLICIES: |
| Last Revised: | Jan. 1, 2025 | 8.01.01 Adoptive Immunotherapy |
| Replaces: | Extracted from 8.01.01 | |

**Select a hyperlink below to be directed to that section.**

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

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## Introduction

The immune system is made up of several different disease-fighting cells. In cancer, however, the immune system sometimes either doesn't work as it should, or the cancer cells are able to hide from the immune system. One therapy that draws on the immune system's natural fighting ability is called adoptive immunotherapy. In this technique, certain types of immune system cells are withdrawn from the person to be treated. They're re-engineered in a lab and given back to the individual in the hope that they will be better able to attack and defeat cancer cells. This is an active area of study. The US Food and Drug Administration has approved four adoptive immunotherapy treatments, Breyanzi (lisocabtagene maraleucel), Kymriah (tisagenlecleucel), Tecartus (brexucabtagene autoleucel), and Yescarta (axicabtagene ciloleucel). The FDA has approved them for people of certain ages who have specific types of cancer. This policy describes when these treatments may be considered medically necessary.

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

## Policy Coverage Criteria

| Treatment | Medical Necessity |
|---|---|
| **Kymriah (tisagenlecleucel) IV** | **Kymriah (tisagenlecleucel) is considered medically necessary for relapsed[a] or refractory[b] individuals with B-cell acute lymphoblastic leukemia (ALL) if they meet all of the following criteria:**<br>• Confirmed diagnosis of CD19-positive B-cell ALL with morphologic bone marrow tumor involvement (≥5% lymphoblasts)<br>• Are up to 25 years old at the time of infusion<br>• Have not received prior treatment with tisagenlecleucel or any other gene therapy or are being considered for treatment with any other gene therapy<br>• Have adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis<br>• Do not have any of the following:<br>  ○ Burkitt lymphoma<br>  ○ Active hepatitis B, C, or any uncontrolled infection<br>  ○ Grade 2 to 4 graft-versus-host disease<br>  ○ Concomitant genetic syndrome associated with bone marrow failure with the exception of Down syndrome<br>  ○ Received allogeneic cellular therapy, such as donor lymphocyte infusion, within 6 weeks prior to tisagenlecleucel infusion<br>  ○ Active central nervous system (see **Related Information**) ALL (i.e., white blood cell count ≥5 cells/µL in cerebrospinal fluid with presence of lymphoblasts).<br><br>**Note:** [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.<br><br>[b] Refractory (resistant) disease is defined as those individuals who fail to obtain complete response with induction therapy, i.e., 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). |

| Treatment | Medical Necessity |
|---|---|
| | **Kymriah (tisagenlecleucel) is considered medically necessary for relapsed or refractory[c] individuals with aggressive types of non-Hodgkin lymphoma (NHL) if they meet all of the following criteria:**<br>• Are adults (age ≥18) at the time of infusion<br>• Histologically confirmed diagnosis of diffuse large B-cell lymphoma (DLBCL), not otherwise specified; high-grade B-cell lymphoma or DLBCL arising from follicular lymphoma<br>• Received adequate prior therapy including all of the following:<br>  ○ Anti-CD20 monoclonal antibody for CD20-positive tumor<br>  ○ Anthracycline-containing chemotherapy regimen<br>  ○ For subjects with transformed follicular lymphoma, prior chemotherapy for follicular lymphoma and subsequently have chemorefractory disease after transformation to diffuse large B-cell lymphoma<br>• Have adequate organ and bone marrow function as determined by the treating oncologist/hematologist<br>• Have not received prior CD19-directed chimeric antigen receptor (CAR) T-cell therapy treatment or any other gene therapy or are being considered for treatment with any other gene therapy<br>**AND**<br>• Do not have primary central nervous system lymphoma<br><br>**Note:** Tisagenlecleucel intravenous infusion is considered **investigational** for the treatment of relapsed or refractory primary mediastinal large B-cell lymphoma.<br><br>[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).<br><br>**Kymriah (tisagenlecleucel) is considered medically necessary for individuals with relapsed or refractory[c] follicular lymphoma if they meet all of the following criteria:**<br>• Are adults (age ≥18) at the time of infusion |

| Treatment | Medical Necessity |
|---|---|
| | • Histologically confirmed diagnosis of follicular lymphoma<br>• Received 2 or more lines of systemic therapy for treatment of follicular lymphoma<br>• Have adequate organ and bone marrow function as determined by the treating oncologist/hematologist<br>• Have not received prior CD19-directed chimeric antigen receptor (CAR) T-cell therapy treatment or any other gene therapy or are being considered for treatment with any other gene therapy<br>**AND**<br>• Do not have primary central nervous system lymphoma<br><br>**Note:** [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). |
| **Yescarta (axicabtagene ciloleucel) IV** | **Yescarta (axicabtagene ciloleucel) is considered medically necessary for individuals with histological confirmed large B-cell lymphoma including transformation from follicular lymphoma if they meet all of the following criteria:**<br>• Are adults (age ≥18) at the time of infusion<br>• Relapsed[d] or refractory[d] within 12 months following completion of first-line chemoimmunotherapy that included rituximab and anthracycline<br>• Have adequate organ and bone marrow function as determined by the treating oncologist/hematologist<br>• 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<br>**AND**<br>• Do not have primary central nervous system lymphoma<br><br>**Note:** [d] Relapsed disease defined as complete remission to first-line therapy followed by biopsy-proven disease relapse; refractory disease is defined as no complete remission to first-line therapy.<br><br>**Yescarta (axicabtagene ciloleucel) is considered medically necessary for relapsed or refractory[c] individuals with** |

| Treatment | Medical Necessity |
| --- | --- |
| | **aggressive types of non-Hodgkin lymphoma (NHL) if they meet all of the following criteria:**<br>• Are adults (age ≥18) at the time of infusion<br>• Histologically confirmed diagnosis of diffuse large B-cell lymphoma (DLBCL), not otherwise specified; or primary mediastinal large B-cell lymphoma or high-grade B-cell lymphoma or DLBCL arising from follicular lymphoma<br>• Received adequate prior therapy including all of the following:<br>  ○ Anti-CD20 monoclonal antibody for CD20-positive tumor<br>  ○ Anthracycline-containing chemotherapy regimen<br>  ○ For subjects with transformed follicular lymphoma, prior chemotherapy for follicular lymphoma and subsequently have chemorefractory disease after transformation to DLBCL<br>• Have adequate organ and bone marrow function as determined by the treating oncologist/hematologist<br>• 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<br>**AND**<br>• Do not have primary central nervous system lymphoma<br><br>**Yescarta (axicabtagene ciloleucel) is considered medically necessary for relapsed or refractory[c] individuals with follicular lymphoma if they meet all of the following criteria:**<br>• Are adults (age ≥18) at the time of infusion<br>• Histologically confirmed diagnosis of follicular lymphoma<br>• Received 2 or more lines of systemic therapy for treatment of follicular lymphoma<br>• Have adequate organ and bone marrow function as determined by the treating oncologist/hematologist<br>• 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<br>**AND**<br>• Do not have primary central nervous system lymphoma |

| Treatment | Medical Necessity |
|---|---|
| | **Note:** [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). |
| **Tecartus (brexucabtagene autoleucel) IV** | **Tecartus (brexucabtagene autoleucel) is considered medically necessary for relapsed or refractory[d] individuals with mantle cell lymphoma if they meet all of the following criteria:**<br>• Are adults (age ≥18) at the time of infusion<br>• Histologically confirmed diagnosis of mantle cell lymphoma<br>• Received adequate prior therapy including anthracycline- or bendamustine-containing chemotherapy, anti-CD20 antibody, and a Bruton tyrosine kinase inhibitor (example ibrutinib or acalabrutinib)<br>• Have adequate organ and bone marrow function as determined by the treating oncologist/hematologist<br>• 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<br><br>**Note:** [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<br><br>**Tecartus (brexucabtagene autoleucel) is considered medically necessary for relapsed[a] or refractory[b] individuals with B-cell acute lymphoblastic leukemia (ALL) if they meet all of the following criteria:**<br>• Confirmed diagnosis of CD19-positive B-cell ALL with morphologic bone marrow tumor involvement (≥5% lymphoblasts)<br>• Are adults (age ≥18) at the time of infusion<br>• Have not received prior treatment with brexucabtagene autoleucel or any other gene therapy or are being considered for treatment with any other gene therapy<br>• Have adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis<br>• Do not have any of the following:<br>  ○ Burkitt lymphoma<br>  ○ Active hepatitis B, C, or any uncontrolled infection |

| Treatment | Medical Necessity |
|---|---|
| | ○ Grade 2 to 4 graft-versus-host disease<br>○ Concomitant genetic syndrome associated with bone marrow failure with the exception of Down syndrome<br>○ Received allogeneic cellular therapy, such as donor lymphocyte infusion, within 6 weeks prior to brexucabtagene autoleucel infusion<br>○ Active central nervous system ALL (i.e., white blood cell count ≥5 cells/µL in cerebrospinal fluid with presence of lymphoblasts)<br><br>**Note:** [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.<br><br>[b] Refractory (resistant) disease is defined as those individuals who fail to obtain complete response with induction therapy, i.e., 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). |
| **Breyanzi (lisocabtagene maraleucel) IV** | **Breyanzi (lisocabtagene maraleucel) is considered medically necessary for relapsed or refractory[a] individuals with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) if they meet all of the following criteria:**<br>• Are adults (age ≥18) at the time of infusion<br>• Histologically confirmed diagnosis of CLL or SLL<br>• Received 2 or more prior lines of therapy for treatment of CLL or SLL including a Bruton tyrosine kinase (BTK) inhibitor (e.g., acalabrutinib, ibrutinib, pirtobrutinib, or zanubrutinib) and a B-cell lymphoma 2 (BCL-2) inhibitor (e.g., venetoclax)<br>• Have adequate organ and bone marrow function as determined by the treating oncologist/hematologist<br>• 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<br><br>**Note:** [a] Relapsed or refractory disease is defined as disease progression after 2 or more lines of prior therapy (which may or may not include therapy supported by autologous cell transplant). |

| Treatment | Medical Necessity |
|---|---|
| | **Breyanzi (lisocabtagene maraleucel) is considered medically necessary for relapsed or refractory[b] individuals with mantle cell lymphoma (MCL) if they meet all of the following criteria:**<br>• Are adults (age ≥18) at the time of infusion<br>• Histologically confirmed diagnosis of MCL<br>• Received 2 or more prior lines of systemic therapy for treatment of mantle cell lymphoma including a Bruton tyrosine kinase inhibitor (e.g., acalabrutinib, pirtobrutinib, or zanubrutinib)<br>• Have adequate organ and bone marrow function as determined by the treating oncologist/hematologist<br>• 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<br><br>**Note:** [b] Relapsed or refractory disease is defined as disease progression after 2 or more lines of systemic therapy (which may or may not include therapy supported by autologous cell transplant).<br><br>**Breyanzi (lisocabtagene maraleucel) is considered medically necessary for relapsed or refractory[c] individuals with follicular lymphoma if they meet all of the following criteria:**<br>• Are adults (age ≥18) at the time of infusion<br>• Histologically confirmed diagnosis of follicular lymphoma<br>• Received 2 or more lines of systemic therapy for treatment of follicular lymphoma<br>• Have adequate organ and bone marrow function as determined by the treating oncologist/hematologist<br>• 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<br>**AND**<br>• Do not have primary central nervous system lymphoma<br><br>**Note:** [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). |

| Treatment | Medical Necessity |
|---|---|
| | **Breyanzi (lisocabtagene maraleucel) is considered medically necessary for relapsed or refractory[d] individuals with aggressive types of non-Hodgkin lymphoma (NHL) if they meet all of the following criteria:**<br>• Are adults (age ≥18) at the time of infusion<br>• Histologically confirmed diagnosis of large B-cell lymphoma (LBCL) including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma); high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B<br>• Meets at least ONE of the following<br>  ○ Refractory[f] to first-line chemoimmunotherapy OR relapse[e] within 12 months of first-line chemoimmunotherapy<br>  ○ Refractory[f] to first-line chemoimmunotherapy OR relapse[e] after first line chemoimmunotherapy AND are not eligible for hematopoietic stem cell transplantation due to comorbidities or age<br>  ○ Relapse[d] or refractory[d] after receiving adequate prior therapy including all of the following:<br>  ▫ Anti-CD20 monoclonal antibody for CD20-positive tumor<br>  ▫ Anthracycline-containing chemotherapy regimen<br>  ▫ For subjects with transformed follicular lymphoma, prior chemotherapy for follicular lymphoma and subsequently have chemorefractory disease after transformation to diffuse large B-cell lymphoma<br>• Have adequate organ and bone marrow function as determined by the treating oncologist/hematologist<br>• 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<br>**AND**<br>• Do not have primary central nervous system lymphoma<br><br>**Note:** [d] 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); [e]Relapsed disease defined as |

| Treatment | Medical Necessity |
|---|---|
| | complete remission to first-line therapy followed by biopsy-proven disease relapse; [f]Refractory disease is defined as no complete remission to first-line therapy. |

| Treatment | Investigational |
|---|---|
| **Other applications** | **Other applications of CAR-T therapy are considered investigational.** |

| Length of Approval | |
|---|---|
| **Approval** | **Criteria** |
| **Initial authorization** | **Breyanzi (lisocabtagene maraleucel), Kymriah (tisagenlecleucel), Tecartus (brexucabtagene autoleucel), or Yescarta (axicabtagene ciloleucel) may be approved as a one-time infusion.** |
| **Re-authorization criteria** | **Repeat treatment of Breyanzi (lisocabtagene maraleucel), Kymriah (tisagenlecleucel), Tecartus (brexucabtagene autoleucel), or Yescarta (axicabtagene ciloleucel) is considered investigational.** |

## Documentation Requirements

**The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:**

**For Kymriah (tisagenlecleucel) for relapsed or refractory individuals with B-cell acute lymphoblastic leukemia:**

- Confirmed diagnosis of B-cell acute lymphoblastic leukemia with CD19 tumor expression
- 25 years of age or younger at the time of infusion
- Have not received prior treatment with tisagenlecleucel or any other gene therapy, nor is being considered for treatment with any other gene therapy
- Have adequate and stable renal, liver, pulmonary, cardiac and bone marrow function with no significant deterioration in organ function expected within 4 weeks after apheresis (collection of blood)
- Do not have any of the following:
    - Burkitt lymphoma

## Documentation Requirements

- Active hepatitis B, C, or any uncontrolled infection
- Grade 2 to 4 graft-versus-host disease
- The presence of a genetic syndrome associated with bone marrow failure, with the exception of Down syndrome
- Received cellular therapy from a donor, such as donor lymphocyte infusion, within 6 weeks prior to tisagenlecleucel infusion
- Active central nervous system acute lymphoblastic leukemia (i.e., white blood cell count 5 or greater cells/µL in cerebrospinal fluid with presence of lymphoblasts)

**For Kymriah (tisagenlecleucel) for relapsed or refractory individuals with aggressive types of non-Hodgkin lymphoma:**

- Adults (age 18 or older) at the time of infusion
- Tissue tests confirm the diagnosis of one of the following:
  - Diffuse large B-cell lymphoma, not otherwise specified, or
  - High-grade B-cell lymphoma, or
  - Diffuse large B-cell lymphoma arising from follicular lymphoma
- Have 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
- Have adequate and stable renal, liver, pulmonary, cardiac 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, nor is being considered for treatment with any other gene therapy
- Do not have primary central nervous system lymphoma

**For Kymriah (tisagenlecleucel) for individuals with relapsed or refractory follicular lymphoma:**

- Are adults (age ≥18) at the time of infusion
- Histologically confirmed diagnosis of follicular lymphoma
- Received 2 or more lines of systemic therapy for treatment of follicular lymphoma
- Have adequate and stable renal, liver, pulmonary, cardiac and bone marrow function as determined by the treating oncologist/hematologist

## Documentation Requirements

- Have not received prior CD19-directed chimeric antigen receptor (CAR) T-cell therapy treatment or any other gene therapy or are being considered for treatment with any other gene therapy
- Do not have primary central nervous system lymphoma

**For Yescarta (axicabtagene ciloleucel) for individuals with histological confirmed large B-cell lymphoma including transformation from follicular lymphoma:**

- Adults (age 18 or older) at the time of infusion
- Relapsed or refractory within 12 months following completion of first-line chemoimmunotherapy that included rituximab and anthracycline
- Have adequate and stable renal, liver, pulmonary, cardiac 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
- Do not have primary central nervous system lymphoma

**For Yescarta (axicabtagene ciloleucel) for relapsed or refractory individuals with aggressive types of non-Hodgkin lymphoma:**

- Adults (age 18 or older) at the time of infusion
- Tissue tests confirm the diagnosis of one of the following:
    - 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
- Have 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
- Have adequate and stable renal, liver, pulmonary, cardiac 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, nor is being considered for treatment with any other gene therapy
- Do not have primary central nervous system lymphoma

## Documentation Requirements

**For Yescarta (axicabtagene ciloleucel) for relapsed or refractory individuals with follicular lymphoma:**

- Adults (age 18 or older) at the time of infusion
- Histologically confirmed diagnosis of follicular lymphoma
- Have received 2 or more lines of systemic therapy
- Have adequate and stable renal, liver, pulmonary, cardiac 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, nor is being considered for treatment with any other gene therapy
- Do not have primary central nervous system lymphoma

**For Tecartus (brexucabtagene autoleucel) for relapsed or refractory mantle cell lymphoma:**

- Are adults (age ≥18) at the time of infusion
- Histologically confirmed diagnosis of mantle cell lymphoma
- Received adequate prior therapy including anthracycline- or bendamustine-containing chemotherapy, anti-CD20 antibody, and a Bruton tyrosine kinase inhibitor (example ibrutinib or acalabrutinib)
- Have adequate and stable renal, liver, pulmonary, cardiac 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

**For Tecartus (brexucabtagene autoleucel) for relapsed or refractory individuals with B-cell acute lymphoblastic leukemia and ALL of the following:**

- Confirmed diagnosis of CD19-positive B-cell acute lymphoblastic leukemia with morphologic bone marrow tumor involvement (≥5% lymphoblasts)
- Are adults (age ≥18) at the time of infusion
- Have not received prior treatment with brexucabtagene autoleucel or any other gene therapy or are being considered for treatment with any other gene therapy
- Have adequate and stable renal, liver, pulmonary, cardiac and bone marrow 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
    - Concomitant genetic syndrome associated with bone marrow failure, with the exception of Down syndrome

## Documentation Requirements

- Received allogeneic cellular therapy, such as donor lymphocyte infusion, within 6 weeks prior to brexucabtagene autoleucel infusion
- Active central nervous system acute lymphoblastic leukemia (i.e., white blood cell count ≥5 cells/µL in cerebrospinal fluid with presence of lymphoblasts)

**For Breyanzi (lisocabtagene maraleucel) for relapsed or refractory individuals with aggressive types of non-Hodgkin lymphoma:**

- Are adults (age ≥18) at the time of infusion
- 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
- Meets at least ONE of the following
  - Refractory to first-line chemoimmunotherapy OR relapse within 12 months of first-line chemoimmunotherapy
  - Refractory to first-line chemoimmunotherapy OR relapse after first line chemoimmunotherapy AND are not eligible for hematopoietic stem cell transplantation due to comorbidities or age
  - Relapse or refractory after receiving 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
- Have adequate and stable renal, liver, pulmonary, cardiac 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
- Do not have primary central nervous system lymphoma

**For Breyanzi (lisocabtagene maraleucel) for relapsed or refractory individuals with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL):**

- Are adults (age ≥18) at the time of infusion
- Histologically confirmed diagnosis of CLL or SLL
- Received 2 or more prior lines of therapy for treatment of CLL or SLL including a Bruton tyrosine kinase (BTK) inhibitor (e.g., acalabrutinib, ibrutinib, pirtobrutinib, or zanubrutinib) and a B-cell lymphoma 2 (BCL-2) inhibitor (e.g., venetoclax)

## Documentation Requirements

- Have adequate and stable renal, liver, pulmonary, cardiac 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

**For Breyanzi (lisocabtagene maraleucel) for relapsed or refractory individuals with mantle cell lymphoma (MCL):**

- Are adults (age ≥18) at the time of infusion
- Histologically confirmed diagnosis of MCL
- Received 2 or more prior lines of systemic therapy for treatment of mantle cell lymphoma including a Bruton tyrosine kinase inhibitor (e.g., acalabrutinib, pirtobrutinib, or zanubrutinib)
- Have adequate and stable renal, liver, pulmonary, cardiac 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

**For Breyanzi (lisocabtagene maraleucel) for relapsed or refractory individuals with follicular lymphoma:**

- Are adults (age ≥18) at the time of infusion
- Histologically confirmed diagnosis of follicular lymphoma
- Received 2 or more lines of systemic therapy for treatment of follicular lymphoma
- Have adequate and stable renal, liver, pulmonary, cardiac 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

# Coding

| Code | Description |
|---|---|
| **CPT** | |
| 0540T | Chimeric antigen receptor T-cell (CAR-T) therapy; CAR-T cell administration, autologous (code termed 12/31/24) |
| 36511 | Therapeutic apheresis; for white blood cells |

| Code | Description |
|---|---|
| 38228 | Chimeric antigen receptor T-cell (CAR-T) therapy; CAR-T cell administration, autologous (new code effective 1/01/2025) |
| **HCPCS** | |
| Q2041 | Axicabtagene ciloleucel (Yescarta), up to 200 million autologous anti-cd19 car positive viable T cells, including leukapheresis and dose preparation procedures, per therapeutic dose |
| Q2042 | Tisagenlecleucel (Kymriah), up to 600 million car-positive viable T cells, including leukapheresis and dose preparation procedures, per therapeutic dose |
| Q2053 | Brexucabtagene autoleucel (Tecartus), up to 200 million autologous anti-cd19 car positive viable T cells, including leukapheresis and dose preparation procedures, per therapeutic dose |
| Q2054 | Lisocabtagene maraleucel (Breyanzi), up to 110 million autologous anti-CD19 CAR-positive viable T cells, including leukapheresis and dose preparation procedures, per therapeutic dose |
| S2107 | Adoptive immunotherapy i.e., development of specific antitumor reactivity (e.g., tumor-infiltrating lymphocyte therapy) per course of treatment |
| **Non-Covered**<br>These codes are not separately reimbursable | |
| 38225 | 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 (new code effective 1/01/2025) |
| 38226 | Chimeric antigen receptor T-cell (CAR-T) therapy; preparation of blood-derived T lymphocytes for transportation (eg, cryopreservation, storage) (new code effective 1/01/2025) |
| 38227 | Chimeric antigen receptor T-cell (CAR-T) therapy; receipt and preparation of CAR-T cells for administration (new code effective 1/01/2025) |
| 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 (code termed 12/31/2024) |
| 0538T | Chimeric antigen receptor T-cell (CAR-T) therapy; preparation of blood-derived T lymphocytes for transportation (e.g., cryopreservation, storage) (code termed 12/31/2024) |
| 0539T | Chimeric antigen receptor T-cell (CAR-T) therapy; receipt and preparation of CAR-T cells for administration (code termed 12/31/2024) |

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## Related Information

Autologous lymphocytes used as part of adoptive immunotherapy may be harvested in a pheresis procedure or may be isolated from resected tumor tissue.

There is a dosing limit of 1 injection per lifetime.

The recommended dosage of tisagenlecleucel (Kymriah) for individuals with B-cell acute lymphoblastic leukemia who are 50 kg or less is 0.2 to $5.0\times10^6$ chimeric antigen receptor–positive viable T cells per kilogram of body weight intravenously; for individuals above 50 kg, dose is 0.1 to $2.5\times10^8$ total chimeric antigen receptor–positive viable T cells (non-weight-based) intravenously.

The recommended target dose of tisagenlecleucel (Kymriah) for individuals with large B-cell lymphoma is 0.6 to $6.0\times10^8$ chimeric antigen receptor–positive viable T cells intravenously.

The recommended target dose of axicabtagene ciloleucel (Yescarta) for individuals with large B-cell lymphoma is $2\times10^6$ CAR-positive viable T cells per kg body weight, with a maximum of $2\times10^8$ chimeric antigen receptor– positive viable T cells intravenously.

The recommended target dose of brexucabtagene autoleucel (Tecartus) for individuals with mantle cell lymphoma is $2\times10^6$ CAR-positive viable T cells per kg body weight, with a maximum of $2\times10^8$ chimeric antigen receptor- positive viable T cells intravenously.

The recommended target dose of brexucabtagene autoleucel (Tecartus) for individuals with B-cell acute lymphoblastic leukemia is $1\times10^6$ CAR-positive viable T cells per kg body weight, with a maximum of $1\times10^8$ chimeric antigen receptor- positive viable T cells intravenously.

The recommended target dose of lisocabtagene maraleucel (Breyanzi) for individuals with large B-cell lymphoma is 50 to $110\times10^6$ CAR-positive viable T cells as single intravenous infusion.

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 (e.g., facial nerve palsy, brain/eye involvement, hypothalamic syndrome)

Tisagenlecleucel (Kymriah), axicabtagene ciloleucel (Yescarta), brexucabtagene autoleucel (Tecartus), and lisocabtagene maraleucel (Breyanzi) have black box warnings because of the risks of cytokine release syndrome and neurologic toxicities that include fatal or life-threatening reactions. These agents should not be administered to individuals with active infection or inflammatory disorders. It is recommended that severe or life-threatening cytokine release syndrome be treated with tocilizumab. Individuals should be monitored for neurologic events after treatment.

Tisagenlecleucel (Kymriah), axicabtagene ciloleucel (Yescarta), brexucabtagene autoleucel (Tecartus), and lisocabtagene maraleucel (Breyanzi) are available only through a restricted program under a risk evaluation and mitigation strategy (REMS) called the Kymriah REMS, Yescarta REMS, Tecartus REMS, and Breyanzi REMS, respectively. The requirements for the REMS components are as follows:

- Health care facilities that dispense and administer these chimeric antigen receptor (CAR) T therapies must be enrolled and comply with the REMS requirements.
- Certified health care facilities must have onsite, immediate access to tocilizumab, and ensure that a minimum of 2 doses are available for each individual for administration within 2 hours of these CAR T, if needed for treatment of cytokine release syndrome.
- Certified health care facilities must ensure that health care providers who prescribe, dispense, or administer these CAR T therapies are trained to manage cytokine release syndrome and neurologic toxicities.

## Consideration of Age

The ages noted in the policy statements are based on the U.S Food Drug Administration (FDA) labeling for these agents.

# Evidence Review

## 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 individual 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 individual 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 US Food and Drug Administration (FDA) for the treatment of lymphoma and leukemia. Tisagenlecleucel (Kymriah) and brexucabtagene autoleucel (Tecartus) are approved for treatment of subsets of individuals with leukemia and lymphoma and axicabtagene ciloleucel (Yescarta) and lisocabtagene maraleucel (Breyanzi) are approved to treat subsets of individuals with lymphoma.

## Background

## 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 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 individuals who fail to obtain a complete response with induction therapy (i.e., 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 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 individuals, Berry et al

(2017) reported a hazard ratio for event-free survival in MRD-negative individuals compared with MRD-positive individuals 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 (US),[2] and approximately 620 pediatric and young adult individuals 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 individuals 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 individuals 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 individuals with ALL who relapse after hematopoietic cell transplantation is 15%.[6]

The 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 individuals treated with 3 or more prior treatments of clofarabine and blinatumomab trial were 62% and 7%, respectively. Nevertheless, treatment options for individuals 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)

Diffuse large B cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin lymphoma (NHL) and accounts for approximately 25% of NHL 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. 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 individuals 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 individuals 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 individuals with a first relapse of DLBCL or primary refractory DLBCL. Approximately 50% of individuals 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] Individuals 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. OS at 1 year is 23% and 16% at year 2. For individuals who relapse after autologous transplantation, options are limited and include allogeneic hematopoietic stem-cell transplantation. However, the procedure can only be performed if the individual 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 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 (MCL)

Mantle cell lymphoma (MCL) is a rare B-cell malignancy classified as an aggressive form of NHL 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 NHL in the US and differs from DLBCL.[20,21,22] In 2018, the overall incidence of MCL in the US was 3,500 with a 5-year and 10-year prevalence of 12,000 and 18,000 cases, respectively. The median age at the time of diagnosis is 68, a majority of individuals are non-Hispanic white males and more than 70% of individuals present with stage IV disease.[23,24] The majority (75%) of cases initially present with lymphadenopathy while presentation is extranodal in the remaining 25%. 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 an individual 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, and bortezomib.

Despite the availability of multiple treatments, MCL is not curable. 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 individuals to guide course of treatment. First-line treatment of MCL can consist of aggressive or less-aggressive therapy, depending on individual status at baseline.[26] It generally consists of chemotherapy in combination with rituximab. Only 30 to 40% of individuals 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 individuals 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, individual 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 individuals 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 individuals. 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 individuals 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 individuals with small lymphocytic lymphoma or follicular lymphoma.

## Follicular lymphoma

Follicular lymphoma is the second most common subtype of NHL and is associated with an excellent prognosis for most individuals with a median OS >20 years.[34,] Approximately 40 to 80% of individuals treated respond to initial chemoimmunotherapy while 10% do not respond (i.e., refractory disease). However, conventional therapy for follicular lymphoma is not curative and most of these individuals ultimately develop progressive disease.[35,] The prevalence of follicular lymphoma in the US 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.[36,] Individuals with advanced-stage follicular lymphoma after 2 or more 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 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 individuals with relapsed or refractory follicular lymphoma and practice varies widely. Individuals 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 individual performance status. Novel FDA approved agents for treatment in the multiple relapse/refractory setting lenalidomide and tazemetostat. The choice is primarily made based on the individual'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 US

As of September 2023, there are four chimeric antigen receptor (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 of Evidence

## Tisagenlecleucel (Kymriah)

For individuals who are up to 25 years of age with relapsed or refractory B-cell ALL who receive tisagenlecleucel, the evidence includes multiple single-arm prospective trials. The relevant outcomes are OS, disease-specific survival (DSS), quality of life (QOL), and treatment-related mortality and morbidity. The pivotal single-arm trial, ELIANA, reported an 81% response rate (measured by complete response or complete remission with incomplete blood count [CRi]) in heavily pretreated (after two or more lines of treatment) individuals. All individuals who achieved a complete response  or CRi were also MRD-negative, which is predictive of survival in ALL individuals. After a median follow-up of 13.1 months, the median duration of response (DOR) was not reached. OS at 1-year,2-year, and 3-year was 76%, 66%, and 63% respectively. 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 (77%) of individuals, and approximately 88% had an adverse event at grade 3 or higher. Tisagenlecleucel was also evaluated for the treatment of adults with relapsed or refractory large B-cell lymphoma who failed first-line chemoimmunotherapy in the randomized controlled BELINDA trial. The primary endpoint of event-free survival was not superior in the tisagenlecleucel treated arm compared to standard salvage therapy. 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 NHL (e.g., DBLCL not otherwise specified, high-grade B-cell lymphoma, transformed follicular lymphoma) who receive tisagenlecleucel, the evidence includes a single-arm prospective trial (JULIET). The

relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The pivotal single-arm trial reported a 52% overall response rate (measured by complete or partial remission) in heavily pretreated individuals. OS at 1-year and 2-year was 49% and 42% respectively. The observed benefits were offset by a high frequency and severity of adverse events. Any grade cytokine release syndrome was observed in 58% of the individuals, and 63% had an adverse event suspected to be related to study drug at grade 3 or higher. 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 who receive tisagenlecleucel, the evidence includes a single-arm prospective trial. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The ELARA study enrolled adult participants 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 98 participants who received axicabtagene ciloleucel, interim data for 90 consecutive participants who completed at least 9 months of follow-up from date of first response was reported with a median follow-up of 9.1months. The primary efficacy analysis demonstrated an overall response rate of 86% with a 68% rate of complete response. The median DOR was not reached. At 12 months, 71% remained event-free. 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 an improvement in the net health outcome.

## Axicabtagene Ciloleucel (Yescarta)

For individuals who are adults with a histologically confirmed diagnosis of aggressive NHL (e.g., 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 two single-arm prospective trial. The relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The pivotal single-arm trial ZUMA-1 after two or more lines of treatment reported an 83% overall response rate (measured by complete or partial remission) in heavily pretreated individuals. OS at 1, 2, and 5 years was 59%,50%, and 49%, respectively. The observed benefits were offset by a high frequency and severity of adverse events. Cytokine release syndrome was observed in more than half of individuals, and 98% had an adverse event at grade 3 or higher. Axicabtagene ciloleucel was also evaluated for the treatment of adults with relapsed or refractory large B-cell lymphoma who failed first-line chemoimmunotherapy in the randomized controlled ZUMA-7 trial. Axicabtagene ciloleucel

treatment resulted in more than 60% improvement in the primary endpoint of event-free survival as well as multiple secondary outcomes such as response rate compared with standard of care. The expected level of high-grade toxic effects were reported. 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 individuals 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 individuals who received axicabtagene ciloleucel, interim data for 81 consecutive individuals 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 overall response rate of 91% with a 60% rate of complete response. The median DOR was not reached. At 12 months, 76% remained in remission. OS at 1-year survival was 93%. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

## Brexucabtagene Autoleucel (Tecartus)

For individuals who are adults with relapsed or refractory MCL who receive brexucabtagene autoleucel, the evidence includes one phase II single-arm study. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The ZUMA-2 study enrolled adult individuals with relapsed refractory MCL who were heavily pre-treated. Of 74 individuals enrolled, therapy was successfully manufactured for 71 (96%) and administered to 68 (92%). The primary efficacy analysis demonstrated an objective response rate of 87% with a 62% rate of complete response. OS at 1-year was 86%. Among individuals who have disease progression after BTK therapy, the reported objective response rate ranges from 25 to 42% with a median OS of 6 to 10 months with salvage therapies. 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 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 ZUMA-3 single-arm trial reported a 52% response rate (measured by complete response or CRi) in heavily pretreated individuals. A majority of individuals who achieved a complete response or complete remission with incomplete blood count were also MRD negative, which is predictive of survival in ALL individuals. OS at 1-year was 71%. The observed benefits seen with brexucabtagene autoleucel

must be balanced with consideration of a high frequency and severity of adverse events. Cytokine release syndrome was observed in more than half (89%) of the individuals and approximately 24% had an adverse event at grade 3 or higher. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

## Lisocabtagene Maraleucel (Breyanzi)

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%). The primary efficacy analysis demonstrated an ORR of 73%. The median DOR was 16.7 months. Response durations were longer in patients who achieved a complete response, as compared to patients with a best response or a partial response. Of the 104 patients who achieved a complete response, 68 (65%) had remission lasting at least 6months and 64 (62%) had remission lasting at least 9 months. One-year survival was 58%. Cytokine release syndrome, including fatal or life-threatening reactions, occurred in 46% of patients, including Grade 3 or higher disease in 4% of patients. Lisocabtagene maraleucel was also evaluated for the treatment of adults with relapsed or refractory large B-cell lymphoma after one prior therapy in the randomized controlled TRANSFORM trial and single-arm study PILOT. The primary endpoint of event free survival in the lisocabtagene maraleucel treated arm was superior to standard therapy (10.1 versus 2.3 months; HR=0.35) in the TRANSFORM trial. The primary endpoint of ORR was 80% in the PILOT trial that enrolled transplant-ineligible patients with relapsed or refractory LBCL after 1 line of chemoimmunotherapy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

## Ongoing and Unpublished Clinical Trials

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

## Table 1. Summary of Key Trials

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| **Ongoing** | | | |
| **Tisagenlecleucel** | | | |
| NCT02445222[a] | CAR-T Long Term Follow Up (LTFU) Study (PAVO) | 1400 | Feb 2036 |
| NCT03876769[a] | Study of Efficacy and Safety of Tisagenlecleucel in HR B-ALL EOC MRD Positive Patients (CASSIOPEIA) | 120 | Oct 2027 |
| NCT05888493[a] | A Phase III Trial Comparing Tisagenlecleucel to Standard of Care (SoC) in Adult Participants With r/r Follicular Lymphoma (LEDA) | 108 | Jan 2029 |
| **Axicabtagene ciloleucel** | | | |
| NCT03761056a (ZUMA-12) | Efficacy and Safety of Axicabtagene Ciloleucel as First-Line Therapy in Participants With High-Risk Large B-Cell Lymphoma | 42 | Nov 2023 |
| NCT05605899[a] (ZUMA-23) | Study to Compare Axicabtagene Ciloleucel With Standard of Care Therapy as First-line Treatment in Participants With High-risk Large B-cell Lymphoma (ZUMA-23) | 300 | Mar 2031 |
| **Brexucabtagene autoleucel** | | | |
| NCT02625480[a] (ZUMA-4) | Study evaluating brexucabtagene autoleucel in pediatric and adolescent participants with r/r ALL or r/r B-cell NHL | 116 | Aug 2027 |
| NCT05537766[a] (ZUMA-25) | Study of Brexucabtagene Autoleucel in Adults With Rare B-cell Malignancies | 170 | Nov 2029 |
| **Lisocabtagene maraleucel** | | | |
| NCT03484702 (TRANSCEND WORLD) | Trial to determine the efficacy and safety of lisocabtagene maraleucel in aggressive B-Cell NHL | 112 | Dec 2023 |
| NCT03575351 (TRANSFORM) | A study to compare the efficacy and safety of lisocabtagene maraleucel to standard of care in high-risk, transplant-eligible r/r aggressive B-cell NHL | 184 | Oct 2023 |

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| NCT04245839 (TRANSCEND FL) | A study to evaluate the efficacy and safety of lisocabtagene maraleucel in r/r indolent B-cell NHL | 213 | Sep 2028 |
| NCT03331198 | Study evaluating safety and efficacy of lisocabtagene maraleucel in subjects with r/r CLL or SLL | 209 | Jul 2026 |
| NCT03743246 | A study to evaluate the safety and efficacy of lisocabtagene maraleucel r/r B-cell ALL and B-cell NHL | 121 | Dec 2024 |
| NCT03744676 (OUTREACH-007) | A safety trial of lisocabtagene maraleucel for r/r) B-cell NHL in the outpatient setting | 80 | Oct 2023 |
| **Unpublished** | | | |
| **Axicabtagene ciloleucel** | | | |
| NCT02926833a (ZUMA-6) | Safety and Efficacy of KTE-C19 in Combination With Atezolizumab in Adults With Refractory Diffuse Large B-Cell Lymphoma | 37 | Aug 2033 |
| NCT04002401a (ZUMA-14) | Safety and Efficacy of Axicabtagene Ciloleucel in Combination With Rituximab in Participants With Refractory Large B-Cell Lymphoma | 27 | June 2036 |

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

## Practice Guidelines and Position Statements

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the policy conclusions.

Guidelines or position statements will be considered for inclusion if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

## National Institute for Health and Care Excellence

### Tisagenlecleucel

On December 21, 2018, the NICE issued a technology appraisal guidance on tisagenlecleucel for treating relapsed or refractory B-cell ALL in people aged up to 25 years.[79] Treatment with tisagenlecleucel is recommended as an option for treating relapsed or refractory B-cell ALL in people aged up to 25 years. It is only recommended if the conditions in the managed access agreement are followed. Key eligibility criteria are summarized below:

- Has relapsed or refractory ALL, defined by 1 of the following criteria:
    - 2nd or more bone marrow relapse following conventional doses of chemotherapy/monoclonal antibody therapy, or
    - Any bone marrow relapse after allogeneic stem cell transplantation (SCT) and if so, a period of 4 months must have passed since time of transplant to planned time of tisagenlecleucel infusion, or
    - Primary refractory disease i.e. not achieving a complete remission after 2 cycles of 1st line standard chemotherapy, or
    - Secondary refractory disease i.e. not achieving a complete remission after 1 cycle of standard chemotherapy for relapsed disease, or
    - If Philadelphia positive ALL, has disease that has failed standard therapy including 2 TKIs or patient is intolerant of TKIs or if TKIs are contraindicated, or
    - Relapsed disease and ineligible for allogeneic SCT due to comorbid disease (but still fit enough for CAR T-cell therapy with tisagenlecleucel) or contraindicated to allogeneic SCT conditioning or lack of a suitable donor or prior SCT.
- Bone marrow with both flow cytometry detectable ALL and CD19 ALL positivity in the bone marrow.
    - Molecularly detectable minimal residual disease is not sufficient to comply with access to tisagenlecleucel.
- Karnofsky (age ≥16 years) or a Lansky (<16 years) performance status of 50% or more.
- Sufficient end organ function to tolerate treatment with tisagenlecleucel.
- Does not have an isolated extramedullary ALL relapse, i.e., if the patient has extramedullary disease, then the patient must also have bone marrow disease.
- Does not have active central nervous system involvement by ALL.

- No previous therapy with any genetically modified autologous T cell immunotherapy.

On March 13, 2019, the NICE issued a technology appraisal guidance on tisagenlecleucel for treating relapsed or refractory DLBCL after two or more systemic therapies.[80] Treatment with tisagenlecleucel is recommended as an option for treating relapsed or refractory DLBCL after two or more systemic therapies. It is only recommended if the conditions in the managed access agreement are followed. Key eligibility criteria are summarized below:

- Patient has a confirmed histological diagnosis of DLBCL or primary mediastinal B-cell lymphoma or transformed follicular lymphoma and the diagnosis has been either made by or reviewed and confirmed by a designated lymphoma stem cell transplant center.
- Patient fulfils 1 of the following clinical scenarios relating to the definition of relapsed or refractory lymphoma:

  Note: Refractory disease is defined as progressive disease or stable disease (lasting <6 months) as best response to last line of therapy, or disease progression within 12 months of stem cell transplantation. Radiotherapy cannot be counted as a line of therapy.

  - Patient has DLBCL and received 2 or more lines of systemic therapy and relapsed after the last line of systemic therapy OR
  - Patient has DLBCL and received 2 or more lines of systemic therapy and was refractory to the last line of systemic therapy OR
  - Patient has primary mediastinal B-cell lymphoma and received 2 or more lines of systemic therapy and relapsed after the last line of systemic therapy OR
  - Patient has primary mediastinal B-cell lymphoma and received 2 or more lines of systemic therapy and was refractory to the last line of systemic therapy OR
  - Patient has transformed follicular lymphoma to DLBCL and received 2 or more lines of systemic therapy since diagnosis of transformation and relapsed after the last line of systemic therapy OR
  - Patient has transformed follicular lymphoma to DLBCL and received 2 or more lines of systemic therapy since diagnosis of transformation and was refractory to the last line of systemic therapy OR

- Patient has transformed follicular lymphoma to DLBCL, received an anthracycline-containing regimen before transformation, and then received 1 or more lines of systemic therapy and was refractory to the last line of systemic therapy

- Patient has been previously treated with a full dose of an anthracycline containing regimen for the lymphoma
- Patient has been previously treated with at least 1 anti-CD20 monoclonal antibody unless there is clear documentation of the determination of CD20 negative disease
- Patient does not have primary central nervous system (CNS) lymphoma
- Patient does not have known active CNS involvement by the lymphoma
- Patient is aged 18 years or older
- Patient has an ECOG performance score of 0 or 1
- No previous therapy with any genetically modified autologous T cell immunotherapy.

**Axicabtagene Ciloleucel**

On January 23, 2019, the NICE issued a technology appraisal guidance on axicabtagene ciloleucel for treating DLBCL and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies.[81] Treatment with axicabtagene ciloleucel is recommended as an option for treating DLBCL and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies. It is only recommended if the conditions in the managed access agreement are followed. Key eligibility criteria are summarized below:

- Patient has a confirmed histological diagnosis of DLBCL or primary mediastinal B-cell lymphoma or transformed follicular lymphoma and the diagnosis has been either made by or reviewed and confirmed by a designated lymphoma stem cell transplant center.
- Patient fulfills 1 of the following clinical scenarios relating to the definition of relapsed or refractory lymphoma:

  Note: Refractory disease is defined as progressive disease or stable disease (lasting <6 months) as best response to last line of therapy, or disease progression within 12 months of stem cell transplantation. Radiotherapy cannot be counted as a line of therapy.

  - Patient has DLBCL and received 2 or more lines of systemic therapy and relapsed after the last line of systemic therapy OR

- Patient has DLBCL and received 2 or more lines of systemic therapy and was refractory to the last line of systemic therapy OR
- Patient has primary mediastinal B-cell lymphoma and received 2 or more lines of systemic therapy and relapsed after the last line of systemic therapy OR
- Patient has primary mediastinal B-cell lymphoma and received 2 or more lines of systemic therapy and was refractory to the last line of systemic therapy OR
- Patient has transformed follicular lymphoma to DLBCL and received 2 or more lines of systemic therapy since diagnosis of transformation and relapsed after the last line of systemic therapy OR
- Patient has transformed follicular lymphoma to DLBCL and received 2 or more lines of systemic therapy since diagnosis of transformation and was refractory to the last line of systemic therapy OR
- Patient has transformed follicular lymphoma to DLBCL, received an anthracycline-containing regimen before transformation, and then received 1 or more lines of systemic therapy and was refractory to the last line of systemic therapy

- Patient has been previously treated with a full dose of an anthracycline containing regimen for the lymphoma
- Patient has been previously treated with at least 1 anti-CD20 monoclonal antibody unless there is clear documentation of the determination of CD20 negative disease
- Patient does not have primary CNS lymphoma
- Patient does not have known active CNS involvement by the lymphoma
- Patient is aged 18 years or older
- Patient has an ECOG performance score of 0 or 1
- No previous therapy with any genetically modified autologous T cell immunotherapy.

**Brexucabtagene Autoleucel**

On February 24, 2021 the NICE issued a technology appraisal guidance on autologous antiCD19-transduced CD3+ cells for treating relapsed or refractory mantle cell lymphoma (MCL).[82] Treatment with autologous anti-CD19-transduced CD3+ cells is recommended as an

option for relapsed or refractory MCL in adults who have previously had a Bruton's TKI. It is only recommended if the conditions in the managed access agreement are followed. Key eligibility criteria are summarized below:

- Patient has a confirmed histological diagnosis of MCL with documentation of either cyclin D1 overexpression or the presence of the translocation t(11:14) and this diagnosis has been confirmed by a designated lymphoma stem cell transplant center.
- Patient has relapsed or refractory MCL defined by 1 of the following:
    - Refractory disease is defined as being either progressive disease as the best response to the last line of systemic therapy or stable disease as the best response after at least 2 cycles of the last line of therapy with stable disease duration lasting no longer than 6 months from the last dose of the last line of systemic therapy
    - Relapsed disease is defined as disease that responded partially or completely to the last line of therapy and has since progressed
    - Progressive disease must be defined radiologically as per RECIST version 1.1 and be based on CT or MRI scans. Progressive disease cannot be defined on just an increased SUV on a PET scan; in such a circumstance, RECIST version 1.1 criteria for progressive disease must be met
- Patient has been previously treated for MCL with 1 of the following cytotoxic chemotherapy regimens: an anthracycline-containing regimen or a bendamustine-containing regimen or a regimen containing high dose cytarabine with or without cisplatin/carboplatin
- Patient has been previously treated with at least 1 anti-CD20 monoclonal antibody unless there is clear documentation of the determination of CD20 negative disease
- Patient has not had SCT or has had an autologous or allogeneic SCT
- Patient has been previously treated for MCL with a BTK inhibitor (such as ibrutinib or acalabrutinib) and the patient progressed either during treatment or following discontinuation of the BTK inhibitor
- Patient has not previously been treated with an anti-CD19 antibody drug conjugate or, if previously treated with an anti-CD19 antibody drug conjugate, that a biopsy of the relapsed/refractory disease has been done and has been shown to be CD19 positive
- Patient does not have known active CNS involvement by the lymphoma

- Patient is aged 18 years or older on the date of approval for autologous anti-CD19-transduced CD3+ cells by the National MCL CAR-T Clinical Panel
- Patient has an ECOG performance score of 0 or 1
- Patient has sufficient end organ function to tolerate treatment with CAR-T cell therapy
- Patient has either had no previous therapy with any genetically modified autologous or allogeneic T cell immunotherapy or the patient has been treated with doses of genetically modified autologous or allogeneic T cell immunotherapy within an abandoned dosing cohort in a first in human dose-escalation phase I clinical trial.

**Lisocabtagene Maraleucel**

As of July 22, 2022, as per the NICE website, the technology appraisal guidance for transplant-eligible relapsed or refractory aggressive B-cell non-Hodgkin lymphomas [ID3887] and for treating relapsed or refractory aggressive B-cell non-Hodgkin lymphoma after 1 systemic treatment [ID3869] is currently under development with no listed date for completion.

## National Comprehensive Cancer Network

Current National Comprehensive Cancer Network (NCCN) guidelines[i,ii] for ALL ( v. 2.2023)[41], recommend (category 2A) tisagenlecleucel as a treatment option for:

- Philadelphia chromosome-positive individuals 26 years or less in age with refractory disease or 2 or more relapses and failure of 2 tyrosine kinase inhibitors.
- Philadelphia chromosome-negative individuals 26 years or less in age with refractory disease or 2 or more relapses.

Current National Comprehensive Cancer Network (NCCN) guidelines for [i,ii] for ALL ( v. 2.2023)[41] recommend (category 2A) brexucabtagene autoleucel as a treatment option for relapsed or refractory

- Philadelphia chromosome-positive adolescent and young adult individuals with refractory disease OR ≥2 relapses and failure of TKIs.
- Philadelphia chromosome-negative adolescent and young adult individuals with refractory disease OR ≥2 relapses.

Current NCCN guidelines for B-cell lymphoma (v.5.2023)[40], recommend (category 1) axicabtagene ciloleucel and lisocabtagene maraleucel (category 2A) with appropriate bridging therapy as a treatment option for relapsed DLBCL < 12 months or primary refractory DLBCL.

Current NCCN guidelines for B-cell lymphoma (v.5.2023)[40] recommend (category 2A) axicabtagene ciloleucel, tisagenlecleucel, or lisocabtagene maraleucel as a third-line and subsequent therapy for DLBCL.

Current NCCN guidelines for B-cell lymphoma (v.5.2023)[40] recommend (category 2A) axicabtagene ciloleucel and tisagenlecleucel as a treatment option for histological transformation of follicular lymphoma or marginal zone lymphoma (all subtypes) to DLBCL after multiple lines of prior therapies which include ≥2 chemo-immunotherapy regimens for the indolent or transformed disease.

Current NCCN guidelines for B-cell lymphoma (v.5.2023)[40] recommend (category 2A) lisocabtagene maraleucel as a treatment option for histological transformation of follicular lymphoma or nodal marginal zone lymphoma to DLBCL after multiple lines of prior therapies which include ≥2 chemo-immunotherapy regimens for the indolent or transformed disease.

Current NCCN guidelines for B-cell lymphoma (v.5.2023) [40] recommend (category 2A) brexucabtagene autoleucel as a treatment option for adult individuals with relapsed or refractory mantle cell lymphoma only after chemoimmunotherapy and BTK inhibitor.

Current NCCN guidelines for B-cell lymphoma (v.5.2023)[40] recommend (category 2A) axicabtagene ciloleucel as a third-line treatment option for adult individuals with follicular lymphoma (grade 1-2) only after 2 or more lines of systemic therapy.

**Note:** [i] Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Acute Lymphoblastic Leukemia (v.2.2023), and B-Cell Lymphomas (v5.2023). © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed Sep 10, 2023. 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

## Medicare National Coverage

The Centers for Medicare & Medicaid Services (CMS) has published a Proposed Decision Memo regarding the use of CAR T-cell therapy for the treatment of cancer.[83] CMS proposes to cover autologous treatment with T-cells expressing at least one CAR through coverage with evidence

development when prescribed by a treating oncologist, performed in a hospital, and when all of the following requirements are met:

- Individual has:
    - relapsed or refractory cancer; and
    - is not currently experiencing any comorbidity that would otherwise preclude benefit.
- The hospital has:
    - a Cellular Therapy Program consisting of an integrated medical team; and
    - a designated care area; and
    - written guidelines for the administration of CAR T-cell therapy for individual communication, monitoring, and transfer to an intensive care unit.
- The treatment meets the criteria in section a or b, below:
    - a) The treatment is an FDA-approved biological, indicated for use in a hospital setting.
    - b) The treatment is an FDA-approved biological, indicated for use identified in the NCCN Drugs and Biologics Compendium.

CMS proposes to non-cover the use of CAR-expressing T-cells for any treatment that does not involve an FDA-approved biological product.

## Regulatory Status

## Tisagenlecleucel (Kymriah; Novartis) Approvals

On August 30, 2017, approved by the FDA for the treatment of individuals up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse.

On May 1, 2018, approved by the FDA 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 May 27, 2022, Novartis was approved for the treatment of adults with relapsed or refractory follicular lymphoma after 2 or more lines of systemic therapy.

## Axicabtagene ciloleucel (Yescarta; Kite Pharma) Approvals

On October 18, 2017, approved by the FDA 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.

On March 5, 2021, approved by the FDA for the treatment of adults with relapsed or refractory follicular lymphoma after 2 or more lines of systemic therapy.

On April 1, 2022, approved by the FDA for the adults individuals with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy.

## Brexucabtagene autoleucel (Tecartus; Kite Pharma) Approvals

On July 24, 2020, approved for the treatment of adult individuals with relapsed or MCL.

On October 1, 2021, approved for the treatment of adult individuals with relapsed or refractory B-cell precursor ALL.

## lisocabtagene maraleucel (Breyanzi; Juno Therapeutics, Inc.) Approvals

On February 5, 2021, approved for the treatment of adult individuals with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including DLBCL not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B.

On June 24, 2022, approved for the treatment of adult patients with large B-cell lymphoma, including DLBCL not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B who have refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy or refractory disease to first-line chemoimmunotherapy or relapse after first line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation due to comorbidities or age.

On March 14, 2024, approved for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have received at

least two prior lines of therapy, including a Bruton tyrosine kinase (BTK) inhibitor and a B-cell lymphoma (BCL-2) inhibitor.

On May 15, 2024, approved for the treatment of adult patients with relapsed or refractory follicular lymphoma who have received two or more prior lines of systemic therapy.

On May 30, 2024, approved for the treatment of adult patients with relapsed or refractory mantle cell lymphoma who have received at least two prior lines of systemic therapy, including a Bruton tyrosine kinase (BTK) inhibitor.

## 2023 Update

Reviewed prescribing information for all drugs in the policy. No new evidence was found that could change the policy statements.

## 2024 Update

Reviewed prescribing information for all drugs in the policy. Clarified that Breyanzi (lisocabtagene maraleucel), Kymriah (tisagenlecleucel), Tecartus (brexucabtagene autoleucel), or Yescarta (axicabtagene ciloleucel) may be approved as a one-time infusion and repeat treatment is considered investigational. Updated Breyanzi (lisocabtagene maraleucel) coverage criteria to include treatment of certain adults with mantle cell lymphoma. Updated Breyanzi (lisocabtagene maraleucel) coverage criteria to include treatment of certain adults with follicular lymphoma. Updated Breyanzi (lisocabtagene maraleucel) coverage criteria to include treatment of certain adults with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

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## History

| Date | Comments |
|---|---|
| 07/01/20 | New policy, approved June 9, 2020, created with literature review through July 2019. Add to Therapy section. FDA-approved tisagenlecleucel and axicabtagene ciloleucel therapies were moved from policy 8.01.01 Adoptive Immunotherapy to create this new standalone policy 8.01.63. |
| 12/01/20 | Interim Review, approved November 10, 2020. Added Tecartus (brexucabtagene autoleucel) for the treatment of MCL. Added HCPCS code J3590 for Tecartus. |
| 01/01/21 | Coding update, Added HCPCS code C9073. |
| 04/01/21 | Coding update, Added term date 4/1/2021 to HCPC C9073 and added new HCPC code Q2053. |
| 07/01/21 | Coding update, Added HCPCS C9076. |
| 08/01/21 | Annual Review, approved July 13, 2021. Policy statements and rationale for lisocabtagene maraleucel were added. Lisocabtagene maraleucel is considered medically necessary for adult patients with specific types of aggressive non-Hodgkin |

| Date | Comments |
|---|---|
| | 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". |
| 10/01/21 | Coding update, Added HCPCS code Q2054. |
| 02/01/22 | Annual Review, approved January 11, 2022. Policy updated with literature review through October 1, 2021; relevant information on brexucabtagene autoleucel for B-cell acute lymphoblastic leukemia was added. Brexucabtagene autoleucel is considered medically necessary for adult patients with relapsed/refractory B-cell acute lymphoblastic leukemia. Removed HCPCS code J3590. |
| 06/01/22 | Interim Review, approved May 10, 2022. Policy statements and rationale for additional indication for axicabtagene ciloleucel were added. Axicabtagene ciloleucel is considered medically necessary for adult patients with relapsed or refractory follicular lymphoma after 2 or more lines of systemic therapy. Removed HCPCS code C9073. |
| 10/01/22 | Interim Review, approved September 13, 2022. Policy updated with literature review through March 15, 2022. Multiple references were added. Policy statements and Rationale for additional indication for axicabtagene ciloleucel were added. Axicabtagene ciloleucel is considered medically necessary for adult individuals with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy. Removed HCPCS code C9076. Changed the wording from "patient" to "individual" throughout the policy for standardization. |
| 12/01/22 | Interim Review, approved November 8, 2022. Policy updated with literature review through July 22, 2022. Multiple references were added. Policy statements and Rationale for additional indication for tisagenlecleucel, axicabtagene ciloleucel and lisocabtagene maraleucel were added. Tisagenlecleucel is considered medically necessary for relapsed or refractory individuals with follicular lymphoma. Axicabtagene ciloleucel is considered medically necessary for adults with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy. Lisocabtagene maraleucel is considered medically necessary for adults with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy or is refractory to first-line chemoimmunotherapy or relapse after first line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation due to comorbidities or age. |
| 09/01/23 | Annual Review, approved August 7, 2023. Reviewed prescribing information for all drugs in the policy. No new evidence was found that could change the policy statements. |
| 03/01/24 | Annual Review, approved February 26, 2024. Policy updated with literature review through September 8, 2023; multiple references were added. Editorial refinements were also made without changing the original intent. No new evidence was found that |

| Date | Comments |
|---|---|
| | could change the policy statements. Moved CPT code 0540T from non-covered section to regular section of coding chart since this is no longer a status B code. |
| 04/01/24 | Interim Review, approved March 25, 2024. Clarified that Breyanzi (lisocabtagene maraleucel), Kymriah (tisagenlecleucel), Tecartus (brexucabtagene autoleucel), or Yescarta (axicabtagene ciloleucel) may be approved as a one-time infusion and repeat treatment is considered investigational. |
| 07/01/24 | Interim Review, approved June 11, 2024. Updated Breyanzi (lisocabtagene maraleucel) coverage criteria to include treatment of certain adults with mantle cell lymphoma. Updated Breyanzi (lisocabtagene maraleucel) coverage criteria to include treatment of certain adults with follicular lymphoma. Updated Breyanzi (lisocabtagene maraleucel) coverage criteria to include treatment of certain adults with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). |
| 01/01/25 | Coding update. Adding new CPT codes 38225-38228 and removed termed codes 0537T-0540T. |



**Scope**: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.