LifeWise
Health Plan of Washington

MEDICAL POLICY – 8.01.63

Chimeric Antigen Receptor Therapy for Leukemia and Lymphoma

BCBSA Ref. Policy:	8.01.63	
Effective Date:	Mar. 1, 2025	RELATED MEDICAL POLICIES:
Last Revised:	April 1, 2025	8.01.01 Adoptive Immunotherapy
Replaces:	Extracted from 8.01.01	

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∞ Clicking this icon returns you to the hyperlinks menu above.

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 In this technique, certain types of immune system cells are withdrawn from the person to be treated.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
Aucatzyl (obecabtagene autoleucel) IV	**Aucatzyl (obecabtagene autoleucel) is considered medically necessary for relapsed[a] or refractory[b] individuals with B-cell acute lymphoblastic leukemia (ALL) when all the following criteria are met:** • The individual is aged 18 years or older **AND** • Has confirmed diagnosis of CD19-positive B-cell ALL with morphologic bone marrow tumor involvement (≥5% lymphoblasts) **AND** • Has not received prior CD19-directed CAR T-cell therapy treatment or any other gene therapy or are being considered for treatment with any other gene therapy **AND** • Has adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis **AND** • 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 obecabtagene autoleucel infusion ○ Active central nervous system (see **Related Information**) ALL (i.e., white blood cell count ≥5 cells/µL in cerebrospinal fluid with presence of lymphoblasts). **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.

Treatment	Medical Necessity
	[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) when all the following criteria are met:** • The individual is aged 18 years or older at the time of infusion **AND** • Has histologically confirmed diagnosis of CLL or SLL **AND** • 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) **AND** • Has adequate organ and bone marrow function as determined by the treating oncologist or hematologist **AND** • Has 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 **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). **Breyanzi (lisocabtagene maraleucel) is considered medically necessary for relapsed or refractory[b] individuals with mantle cell lymphoma (MCL) when all the following criteria are met:** • The individual is aged 18 years or older at the time of infusion **AND** • Has histologically confirmed diagnosis of MCL **AND** • Received 2 or more prior lines of systemic therapy for treatment of mantle cell lymphoma including a Bruton tyrosine

Treatment	Medical Necessity
	kinase inhibitor (e.g., acalabrutinib, pirtobrutinib, or zanubrutinib) **AND** • Has adequate organ and bone marrow function as determined by the treating oncologist or hematologist **AND** • Has 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 **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). **Breyanzi (lisocabtagene maraleucel) is considered medically necessary for relapsed or refractory[c] individuals with follicular lymphoma when all the following criteria are met:** • The individual is aged 18 years or older at the time of infusion **AND** • Has histologically confirmed diagnosis of follicular lymphoma **AND** • Received 2 or more lines of systemic therapy for treatment of follicular lymphoma **AND** • Has adequate organ and bone marrow function as determined by the treating oncologist or hematologist **AND** • Has not received prior CD19-directed CAR T-cell therapy treatment or any other gene therapy or are being considered for treatment with any other gene therapy **AND** • Do not have primary central nervous system lymphoma **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) when all the following criteria are met: • The individual is aged 18 years or older at the time of infusion **AND** • Has 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 **AND** • Meets at least ONE of the following ○ Refractory[f] to first-line chemoimmunotherapy OR relapse[e] within 12 months of first-line chemoimmunotherapy ○ 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 ○ Relapse[d] or refractory[d] 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 **AND** • Has adequate organ and bone marrow function as determined by the treating oncologist or hematologist **AND** • Has not received prior CD19-directed CAR T-cell therapy treatment or any other gene therapy or are being considered for treatment with any other gene therapy **AND**

Treatment	Medical Necessity
	• Do not have primary central nervous system lymphoma **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 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.

Kymriah (tisagenlecleucel) IV	**Kymriah (tisagenlecleucel) is considered medically necessary for relapsed[a] or refractory[b] individuals with B-cell acute lymphoblastic leukemia (ALL) when all the following criteria are met:**
	• The individual is aged up to 25 years at the time of infusion
	AND
	• Has confirmed diagnosis of CD19-positive B-cell ALL with morphologic bone marrow tumor involvement (≥5% lymphoblasts)
	AND
	• Has not received prior CD19-directed CAR T-cell therapy treatment or any other gene therapy or are being considered for treatment with any other gene therapy
	AND
	• Has adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis
	AND
	• 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 tisagenlecleucel infusion
	  ○ Active central nervous system (see **Related Information**) ALL (i.e., white blood cell count ≥5 cells/µL in cerebrospinal fluid with presence of lymphoblasts).

Treatment	Medical Necessity
	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. [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). **Kymriah (tisagenlecleucel) is considered medically necessary for relapsed or refractory[c] individuals with aggressive types of non-Hodgkin lymphoma (NHL) when all the following criteria are met:** • The individual is aged 18 or older at the time of infusion **AND** • Has histologically confirmed diagnosis of diffuse large B-cell lymphoma (DLBCL), not otherwise specified; high-grade B-cell lymphoma or DLBCL arising from follicular lymphoma **AND** • Received adequate prior therapy including all the following: o Anti-CD20 monoclonal antibody for CD20-positive tumor o Anthracycline-containing chemotherapy regimen o For subjects with transformed follicular lymphoma, prior chemotherapy for follicular lymphoma and subsequently have chemorefractory disease after transformation to diffuse large B-cell lymphoma **AND** • Has adequate organ and bone marrow function as determined by the treating oncologist or hematologist **AND** • Has 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 **AND** • Do not have primary central nervous system lymphoma

Treatment	Medical Necessity
	Note: Tisagenlecleucel intravenous infusion is considered **investigational** for the treatment of relapsed or refractory primary mediastinal large B-cell lymphoma. [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). **Kymriah (tisagenlecleucel) is considered medically necessary for individuals with relapsed or refractory[c] follicular lymphoma when all the following criteria are met:** • The individual is aged 18 years or older at the time of infusion **AND** • Has histologically confirmed diagnosis of follicular lymphoma **AND** • Received 2 or more lines of systemic therapy for treatment of follicular lymphoma **AND** • Has adequate organ and bone marrow function as determined by the treating oncologist or hematologist **AND** • Has 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 **AND** • Do not have primary central nervous system lymphoma **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 when all the following criteria are met:** • The individual is aged 18 years or older at the time of infusion **AND**

Treatment	Medical Necessity
	• Has histologically confirmed diagnosis of mantle cell lymphoma **AND** • Received adequate prior therapy including anthracycline- or bendamustine-containing chemotherapy, anti-CD20 antibody, and a Bruton tyrosine kinase inhibitor (example ibrutinib or acalabrutinib) **AND** • Has adequate organ and bone marrow function as determined by the treating oncologist or hematologist **AND** • Has 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 **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 **Tecartus (brexucabtagene autoleucel) is considered medically necessary for relapsed[a] or refractory[b] individuals with B-cell acute lymphoblastic leukemia (ALL) when all the following criteria are met:** • The individual is aged 18 years or older at the time of infusion **AND** • Has confirmed diagnosis of CD19-positive B-cell ALL with morphologic bone marrow tumor involvement (≥5% lymphoblasts) **AND** • Has not received prior CD19-directed CAR T-cell therapy treatment or any other gene therapy or are being considered for treatment with any other gene therapy **AND** • Has adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis **AND** • Do not have any of the following: ○ Burkitt lymphoma

Treatment	Medical Necessity
	○ 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 ALL (i.e., white blood cell count ≥5 cells/µL in cerebrospinal fluid with presence of lymphoblasts) **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. [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).
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 when all the following criteria are met:** • The individual is aged 18 years or older at the time of infusion **AND** • Has relapsed[d] or refractory[d] within 12 months following completion of first-line chemoimmunotherapy that included rituximab and anthracycline **AND** • Has adequate organ and bone marrow function as determined by the treating oncologist or hematologist **AND** • Has not received prior CD19-directed CAR T-cell therapy treatment or any other gene therapy or are being considered for treatment with any other gene therapy **AND** • Do not have primary central nervous system lymphoma

Treatment	Medical Necessity

	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.
	
	Yescarta (axicabtagene ciloleucel) is considered medically necessary for relapsed or refractory[c] individuals with aggressive types of non-Hodgkin lymphoma (NHL) when all the following criteria are met:
	• The individual is aged 18 years or older at the time of infusion
	AND
	• Has 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
	AND
	• Received adequate prior therapy including all 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 DLBCL
	AND
	• Has adequate organ and bone marrow function as determined by the treating oncologist or hematologist
	AND
	• Has not received prior CD19-directed CAR T-cell therapy treatment or any other gene therapy or are being considered for treatment with any other gene therapy
	AND
	• Do not have primary central nervous system lymphoma
	
	Yescarta (axicabtagene ciloleucel) is considered medically necessary for relapsed or refractory[c] individuals with follicular lymphoma when all the following criteria are met:
	• The individual is aged 18 years or older at the time of infusion

Treatment	Medical Necessity
	AND • Has histologically confirmed diagnosis of follicular lymphoma **AND** • Received 2 or more lines of systemic therapy for treatment of follicular lymphoma **AND** • Has adequate organ and bone marrow function as determined by the treating oncologist or hematologist **AND** • Has not received prior CD19-directed CAR T-cell therapy treatment or any other gene therapy or are being considered for treatment with any other gene therapy **AND** • Do not have primary central nervous system lymphoma **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	Investigational
Other applications	**The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.** **Other applications of CAR-T therapy are considered investigational.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**Non-formulary exception reviews for all drugs listed in the policy may be approved up to 12 months.** **All other reviews for Aucatzyl (obecabtagene autoleucel), Breyanzi (lisocabtagene maraleucel), Kymriah (tisagenlecleucel), Tecartus (brexucabtagene autoleucel), or**

Length of Approval	
Approval	**Criteria**
	Yescarta (axicabtagene ciloleucel) may be approved as a one-time infusion.
Re-authorization criteria	**Repeat treatment of Aucatzyl (obecabtagene autoleucel), 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 Aucatzyl (obecabtagene autoleucel) for relapsed or refractory individuals with B-cell acute lymphoblastic leukemia:

- Confirmed diagnosis of B-cell acute lymphoblastic leukemia with CD19 tumor expression
- Adults (aged 18 years or older) at time of infusion
- Have not received prior CD-19 directed CAR T-cell therapy treatment 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
    - 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 (aged 18 years or older) at the time of infusion

Documentation Requirements

- 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 (aged 18 years or older) 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 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 (aged 18 years 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

Documentation Requirements

- 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 (aged 18 years 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

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

- Adults (aged 18 years 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 (aged 18 years or older) at the time of infusion
- Histologically confirmed diagnosis of mantle cell lymphoma

Documentation Requirements

- 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 (aged 18 years or older) at the time of infusion
- Have not received prior CD-19 directed CAR T-cell therapy treatment 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
    - 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 (aged 18 years or older) 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

Documentation Requirements

  - 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 (aged 18 years or older) 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)
- 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 (aged 18 years or older) 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

Documentation Requirements

- 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 (aged 18 years or older) 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
38228	Chimeric antigen receptor T-cell (CAR-T) therapy; CAR-T cell administration, autologous (new code effective 01/01/25)
HCPCS	
C9301	Obecabtagene autoleucel, up to 410 million cd19 car-positive viable t cells, including leukapheresis and dose preparation procedures (Aucatzyl), per therapeutic dose (new code effective 04/01/25)
C9399	Unclassified drugs or biologicals (use to report: Aucatzyl)
J3590	Unclassified biologics (use to report: Aucatzyl)
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

Code	Description
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

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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 5.0×10^6 chimeric antigen receptor–positive viable T cells per kilogram of body weight intravenously; for individuals above 50 kg, dose is 0.1 to 2.5×10^8 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 6.0×10^8 chimeric antigen receptor–positive viable T cells intravenously.

The recommended target dose of axicabtagene ciloleucel (Yescarta) for individuals with large B-cell lymphoma is 2×10^6 CAR-positive viable T cells per kg body weight, with a maximum of 2×10^8 chimeric antigen receptor– positive viable T cells intravenously.

The recommended target dose of brexucabtagene autoleucel (Tecartus) for individuals with mantle cell lymphoma is 2×10^6 CAR-positive viable T cells per kg body weight, with a maximum of 2×10^8 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 1×10^6 CAR-positive viable T cells per kg body weight, with a maximum of 1×10^8 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 110×10^6 CAR-positive viable T cells as single intravenous infusion.

The recommended target dose of obecabtagene autoleucel (Aucatzyl) for individuals with B-cell acute lymphoblastic leukemia is 410×10^6 CD19 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.

Obecabtagene autoleucel (Aucatzyl)

The ALLCAR19 trial (NCT02935257) is a Phase 1 trial evaluating Aucatzyl in adults with relapsed or refractory (R/R) B-cell acute lymphoblastic leukemia (ALL). Because adult individuals with R/R B-cell ALL are more susceptible to immune-related toxic effects, a bone marrow burden–guided split-dose regimen was introduced as proof of concept. This split-dose regimen was then also implemented into the FELIX trial. The FELIX trial (NCT04404660) was a pivotal registrational Phase 1b/2, open-label, multicenter, single-arm trial that evaluated the safety and efficacy of Aucatzyl: Phase 1b included two groups: (1) 1A, individuals with morphologic disease (≥5% bone marrow blasts) and (2) 1B, individuals with minimal residual disease (MRD; <5% bone marrow blasts) and Phase 2 consisted of the primary pivotal group (2A), including individuals with morphologic disease at enrollment. Additionally, two exploratory groups were included: (1) 2B, individuals with MRD and (2) 2C, individuals with isolated extramedullary disease. Eligible individuals were adults with R/R B-cell ALL, defined by any of the following: first relapse following a remission lasting ≤12 months, R/R ALL after ≥2 prior lines of systemic therapy, or R/R ALL ≥3 months after allogeneic stem cell transplantation (SCT) and disease burden of ≥5% blasts in bone marrow at screening. Among individuals in the efficacy-evaluable population who achieved best response of complete remission (CR) "at any time" (N = 33; 51%), the median duration for remission (mDOR) was 14.1 months (95% CI: 6.1, not reached [NR]). Among individuals in the efficacy-evaluable population in whom best response was CR with incomplete hematologic recovery "at any time" (N = 8; 12%), mDOR was 10.5 months (95% CI: 1.8, NR). Any-grade cytokine release syndrome (CRS) occurred in 75% of individuals; grade ≥3 CRS occurred in 3%. The median time to onset of CRS occurred 8 days after infusion (Days 1–23), with a median duration of 5 days (Days 1–21). Tocilizumab was used to manage CRS in 73% of individuals, and glucocorticoids were used in 21%. Any-grade neurologic toxicities occurred in 64% of individuals; grade ≥3 occurred in 12%, including immune effector cell-associated neurotoxicity syndrome (ICANS) in 24% (grade ≥3, 7%). The median time to onset of ICANS after the first infusion was 8 days (Days 1–10), with a median duration of 8.5 days (Days 1–53). Glucocorticoids were used to manage ICANS in many of the individuals. Additional grade 3 adverse events (AEs) included infections – pathogen unspecified (31%) and febrile neutropenia (26%).

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			
NCT03761056[a] **(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			

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT03743246	A study to evaluate the safety and efficacy of lisocabtagene maraleucel r/r B-cell ALL and B-cell NHL	21	Jan 2026
Unpublished			
Axicabtagene ciloleucel			
NCT02926833[a] (ZUMA-6)	Safety and Efficacy of KTE-C19 in Combination With Atezolizumab in Adults With Refractory Diffuse Large B-Cell Lymphoma	37	Aug 2033
NCT04002401[a] (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 May 15, 2024, the National Institute for Health and Care Excellence (NICE) issued a technology appraisal guidance [TA975] on tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukemia (ALL) in people aged 25 years and under. Treatment with

tisagenlecleucel is recommended as an option for treating relapsed or refractory B-cell ALL that is

- relapsed after a transplant, or
- relapsed for a second or later time, or
- refractory

On November 29, 2023, the NICE issued a technology appraisal guidance [TA933] and stated that it is unable to make a recommendation on tisagenlecleucel (Kymriah) for treating relapsed or refractory diffuse large B-cell lymphoma in adults after 2 or more systemic therapies because Novartis did not provide a complete evidence submission.

Axicabtagene Ciloleucel

On February 28, 2023, the NICE issued a technology appraisal guidance [TA872] on axicabtagene ciloleucel for treating DLBCL and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies. 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. The committee concluded that axicabtagene ciloleucel would be positioned as a treatment option for people whose disease:

- did not respond after 2 systemic therapies, or
- has relapsed after 1 systemic therapy, and who have had chemotherapy and an autologous stem cell transplant but whose disease has then relapsed again, or
- has relapsed after 1 systemic therapy, and who would have been able to have an autologous stem cell transplant as part of a second treatment, but whose disease does not respond to salvage chemotherapy

On June 7, 2023, the NICE issued a technology appraisal [TA895] guidance on axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after first-line chemoimmunotherapy. Treatment with axicabtagene ciloleucel is recommended as an option for treating diffuse large B-cell lymphoma in adults if the conditions in the managed access agreement are followed. Relapsed or refractory was defined as follows:

- Refractory disease is defined as progressive disease as the best response to 1st line standard chemo-immunotherapy or stable disease as the best response after at least 4 cycles of 1st line standard chemo-immunotherapy or a partial response as the best response after at least 6 cycles of 1st line standard chemo-immunotherapy with biopsy-proven residual disease or a

partial response with biopsy-proven progressive disease within 12 months or less from completion of treatment.
- Relapsed disease is defined as disease that was in complete remission following 1st line standard chemo-immunotherapy and has been followed by a biopsy-proven disease relapse within 12 months or less from completion of treatment

On June 7, 2023, the NICE issued a technology appraisal guidance [TA894] on axicabtagene ciloleucel for treating relapsed or refractory follicular lymphoma. Axicabtagene ciloleucel is not recommended, within its marketing authorization, for treating relapsed or refractory follicular lymphoma after 3 or more systemic treatments in adults. The committee made these recommendations because the clinical evidence is from a small study that suggests that axicabtagene ciloleucel increases the amount of time people have before their condition gets worse and how long they live, but it is uncertain by how much. Axicabtagene ciloleucel does not meet NICE's criteria to be considered a life-extending treatment at the end of life. This is because people having standard treatments for relapsed or refractory follicular lymphoma after 3 or more systemic treatments are likely to live longer than 2 years.

Brexucabtagene Autoleucel

On February 24, 2021 the NICE issued a technology appraisal guidance [TA677] on brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma (MCL).[91,] Treatment with brexucabtagene autoleucel 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. Relapsed or refractory was defined as follows:

- 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

On June 7, 2023 the NICE issued a technology appraisal guidance [TA893] on brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over. [92,]Treatment with brexucabtagene autoleucel is recommended as an option for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and

over. It is only recommended if the conditions in the managed access agreement are followed. Relapsed or refractory was defined as follows:

- The individual fulfils one of the following clinical scenarios relating to the definition of relapsed or refractory ALL.
    - the individual has primary refractory disease i.e. did not achieve a complete remission after 2 cycles of standard chemotherapy for newly diagnosed ALL or,
    - the individual has a bone marrow relapse after allogeneic stem cell transplantation in 1st remission and is at least 3 months since allogeneic SCT with no active Graft versus Host Disease (GVHD) requiring systemic therapy or,
    - the individual has a bone marrow relapse after allogeneic stem cell transplantation in 2nd remission and is at least 3 months since allogeneic SCT with no GvHD requiring systemic therapy or,
    - the individual is in 1st bone marrow relapse following a remission lasting 12 months or less (not had SCT) or,
    - the individual is refractory to or has relapsed after 2nd or more line chemotherapy/monoclonal antibody (not had SCT) or,
    - relapsed disease and ineligible for allogeneic SCT due to comorbid disease (but still fit enough for CAR-T cell therapy with brexucabtagene autoleucel) or contraindicated to allogeneic SCT conditioning or lack of a suitable donor.

Lisocabtagene Maraleucel

On July 10, 2024, the NICE issued a technology appraisal guidance [TA987] and stated that it is unable to make a recommendation on lisocabtagene maraleucel (Breyanzi) for treating relapsed or refractory aggressive B-cell non-Hodgkin lymphoma in adults because Celgene did not provide a complete evidence submission.

As of September 3, 2024, as per the NICE website, the technology appraisal guidance "Lisocabtagene maraleucel 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.

As of September 3, 2024, as per the NICE website, the technology appraisal guidance "Lisocabtagene maraleucel for treating relapsed or refractory chronic lymphocytic leukaemia or small lymphocytic lymphoma [ID6174]" is currently under development with no listed date for completion.

National Comprehensive Cancer Network

Acute Lymphoblastic Leukemia

Current National Comprehensive Cancer Network (NCCN) guidelines[i,ii] for ALL (v. 2.2024) recommend (category 2A) tisagenlecleucel as a treatment option for relapsed or refractory

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

Current National Comprehensive Cancer Network (NCCN) guidelines[i,ii] for ALL (v. 2.2024) 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 tyrosine kinase inhibitors.
- Philadelphia chromosome-negative adolescent and young adult individuals with refractory disease OR ≥2 relapses.

B-Cell Lymphoma

Current NCCN guidelines[i,ii] for B-cell lymphoma (v.3.2024) recommend:

- axicabtagene ciloleucel, lisocabtagene maraleucel and tisagenlecleucel (category 2A) as a third-line treatment and subsequent therapy for follicular lymphoma.
- axicabtagene ciloleucel (category 2A) as a third-line treatment and subsequent therapy for marginal zone lymphomas.
- brexucabtagene autoleucel and lisocabtagene maraleucel (category 2A) as a second-line treatment and subsequent therapy for mantle cell lymphoma.
- axicabtagene ciloleucel and lisocabtagene maraleucel (category 1) as a second-line treatment for relapsed disease <12 months or primary refractory diffuse large B-Cell lymphoma.
- lisocabtagene maraleucel (category 2A) as a second-line treatment for diffuse large B-Cell lymphoma when there is no intention to proceed to transplant.
- axicabtagene ciloleucel, lisocabtagene maraleucel and tisagenlecleucel (category 2A) as a third-line treatment and subsequent therapy for diffuse large B-Cell lymphoma.

- axicabtagene ciloleucel, lisocabtagene maraleucel and tisagenlecleucel (category 2A) as a treatment for histologic transformation of indolent lymphomas to diffuse large B-Cell lymphoma after multiple lines of prior therapies that includes ≥2 of chemoimmunotherapy regimens for indolent or transformed disease.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Current NCCN guidelines [i,ii] for chronic lymphocytic leukemia/small lymphocytic lymphoma (v.1.2025) recommend lisocabtagene maraleucel (category 2A) as a treatment option for relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma after prior therapy with BTK inhibitor and venetoclax-based regimens.

Note: [i] Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Acute Lymphoblastic Leukemia (v.3.2024), and B-Cell Lymphomas (v1.2025). National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed February 4, 2025. 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

Decision Summary:

- The Centers for Medicare & Medicaid Services (CMS) covers autologous treatment for cancer with T-cells expressing at least one chimeric antigen receptor (CAR) when administered at healthcare facilities enrolled in the FDA risk evaluation and mitigation strategies (REMS) and used for a medically accepted indication as defined at Social Security Act section 1861(t)(2) i.e., is used for either an FDA-approved indication (according to the FDA-approved label for that product), or for other uses when the product has been FDA-approved and the use is supported in one or more CMS-approved compendia.
- The use of non-FDA-approved autologous T-cells expressing at least one CAR is non-covered. Autologous treatment for cancer with T-cells expressing at least one CAR is non-covered when the requirements in Section A are not met.
- This policy continues coverage for routine costs in clinical trials that use CAR T-cell therapy as an investigational agent that meet the requirements listed in NCD 310.1.

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.

- The FDA, under the accelerated approval regulations, requires that Novartis conduct a randomized phase 3 trial in adult individuals with relapsed or refractory follicular lymphoma. Individuals will be randomized to tisagenlecleucel or an investigator's choice of regimens consistent with the standard of care. The primary endpoint will be progression-free survival with secondary endpoints that include overall survival and objective response rate. The expected date of trial completion is March 31, 2028 and final report submission to the FDA by September 30, 2028.

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.

- The FDA, under the accelerated approval regulations, requires that Kite Pharma conduct a randomized phase 3 trial of axicabtagene ciloleucel in individuals with relapsed or refractory follicular lymphoma. Individuals will be randomized to axicabtagene ciloleucel or to an investigator's choice of regimens consistent with the standard of care. The primary endpoint will be progression-free survival, with secondary endpoints that include objective response rate and overall survival. The expected date of trial completion is June 30, 2027 and final report submission to the FDA by September 30, 2027.

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 refractory MCL. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial.

- The FDA, under the accelerated approval regulations, requires that Kite Pharma conduct a study of brexucabtagene autoleucel treatment of subjects with relapsed or refractory MCL who have not been exposed to a BTK inhibitor. A cohort of subjects naïve to BTK inhibitor therapy will be added to the ongoing ZUMA-2 study to fulfill this requirement. Eighty-six subjects will be enrolled. The primary efficacy endpoint will be objective response rate with a supportive efficacy endpoint of duration of response based on a minimum follow-up of 18 months after first objective disease response. The expected date of trial completion is April 30, 2025 and final report submission to the FDA by October 31, 2025.

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 individuals 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 adult individuals with relapsed or refractory CLL or SLL who have received at least 2 prior lines of therapy, including a BTK inhibitor and a B-cell lymphoma 2 inhibitor. This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

- The FDA, under the accelerated approval regulations, requires that Juno Therapeutics conduct a single arm study of lisocabtagene maraleucel in individuals with relapsed or refractory CLL or SLL who have received at least 2 prior lines of therapy, including a prior BTK inhibitor and a BCL-2 inhibitor, to evaluate overall response rate and durability. The study must include a total of 50 treated individuals and durable response should be based on a minimum follow-up of 15 months after first objective disease response. The expected date of trial completion is March 31, 2027 and final report submission to the FDA by May 31, 2027.

On May 15, 2024, approved for adults with relapsed or refractory follicular lymphoma who have received two or more prior lines of systemic therapy. This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

- The FDA, under the accelerated approval regulations, requires that Juno Therapeutics collect and submit the final report, including datasets from the TRANSCEND FL clinical trial (NCT04245839) to verify and describe the clinical benefit of lisocabtagene maraleucel in adult individuals with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy (including an anti-CD20 antibody and an alkylating agent). All partial and complete responders should have completed at least 24 months of follow up starting from the initial objective response. The expected date of trial completion is May 31, 2025 and final report submission to the FDA by August 31, 2025.

On May 30, 2024, approved for adult individuals with relapsed or refractory MCL who have received at least two prior lines of systemic therapy, including a BRK 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).

2025 Update

Reviewed prescribing information for all drugs in the policy. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Added coverage criteria for Aucatzyl (obecabtagene autoleucel) for certain individuals with acute lymphoblastic leukemia (ALL).

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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 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".

Date	Comments
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 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

Date	Comments
	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.
03/01/25	Annual Review, approved February 11, 2025. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Added coverage criteria for Aucatzyl (obecabtagene autoleucel) for certain individuals with acute lymphoblastic leukemia (ALL). Removed all status B codes from policy (38225-38227 and 0537T-0539T. There is a payment policy addressing all status B codes. Added HCPCS codes C9399 and J3590 to report Aucatzyl.
04/01/25	Coding update. Added new HCPCS code C9301.

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.