BlueCross BlueShield Arizona

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EVIDENCE-BASED CRITERIA	**ORIGINAL EFFECTIVE DATE: 09/28/21**
SECTION: SPECIALTY MEDICAL DRUGS	**LAST REVIEW DATE: 08/15/24**
	CURRENT EFFECTIVE DATE: 08/15/24
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NEXT REVIEW DATE: 3RD QTR 2025	**ARCHIVE DATE:**

CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY FOR LEUKEMIA AND LYMPHOMA

- **BREYANZI® (lisocabtagene maraleucel)**
- **KYMRIAH™ (tisagenlecleucel)**
- **TECARTUS™ (brexucabtagene autoleucel)**
- **YESCARTA™ (axicabtagene ciloleucel)**

Non-Discrimination Statement and Multi-Language Interpreter Services information are located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Evidence-Based Criteria must be read in its entirety to determine coverage eligibility, if any.

This Evidence-Based Criteria provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Evidence-Based Criteria are subject to change as new information becomes available.

For purposes of this Evidence-Based Criteria, the terms "experimental" and "investigational" are considered to be interchangeable.

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CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY FOR LEUKEMIA AND LYMPHOMA

Criteria:

Refer to FDA website for current indications and dosage.

BREYANZI (lisocabtagene maraleucel)

- **Criteria for therapy:** Breyanzi (lisocabtagene maraleucel) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist.

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of **ONE** of the following:

   - Relapsed or refractory 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
   - Relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have received at least 2 prior lines of therapy, including a Bruton tyrosine kinase (BTK) inhibitor and a B-cell lymphoma 2 (BCL-2) inhibitor
   - Relapsed or refractory follicular lymphoma (FL) who have received 2 or more lines of systemic therapy
   - Relapsed or refractory mantle cell lymphoma (MCL) who have received at least 2 prior lines of systemic therapy, including a Bruton tyrosine kinase (BTK) inhibitor
   - Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

4. **For large B-cell lymphoma indication**

   - Individual meets **ALL** of the following:

     a. Disease is classified as **ONE** of the following:

        i. Refractory disease to first line chemoimmunotherapy or relapse within 12 months of first line chemoimmunotherapy
        ii. Refractory disease to first line chemoimmunotherapy or relapse after first line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age
        iii. Relapsed or refractory disease after two or more lines of systemic therapy

b. Has received prior chemotherapy regimen that included an anti-CD20 monoclonal antibody (e.g., obinutuzumab, ofatumumab, or rituximab) and at least one anthracycline (e.g., doxorubicin or pegylated liposomal doxorubicin), unless contraindicated

5. **For CLL or SLL indication**

   - Individual has received at least 2 or more prior regimens that must include:

     a. Bruton Tyrosine Kinase (BTK) inhibitor (e.g., acalabrutinib, ibrutinib, or zanubrutinib)
     b. B-cell lymphoma 2 (BCL-2) inhibitor (e.g., venetoclax)

6. **For follicular lymphoma indication**

   - Individual received at least 2 or more prior regimens that must include:

     a. Anti-CD20 monoclonal antibody (e.g., obinutuzumab, ofatumumab, or rituximab)
     b. Alkylating agent (e.g., bendamustine, cyclophosphamide, chlorambucil, etc.)

7. **For mantle cell lymphoma indication**

   - Individual has received at least 2 or more regimens that must include:

     a. Anti-CD20 monoclonal antibody therapy (e.g., obinutuzumab, ofatumumab, or rituximab)
     b. Bruton Tyrosine Kinase (BTK) inhibitor (e.g., acalabrutinib, ibrutinib, or zanubrutinib)
     c. Alkylating agent (e.g., cyclophosphamide, chlorambucil, platinum based, etc.)

8. Individual meets **ALL** of the following:

   - There is a negative pregnancy test in a woman of childbearing potential
   - Eastern Cooperative Oncology Group (ECOG) performance status is 0 or 1

9. Individual has an absence of **ALL** of the following:

   - Prior CAR T-cell therapy or any other gene therapy or is being considered for treatment with any other gene therapy
   - Clinically significant active systemic fungal, bacterial, viral (hepatitis B, C, or other viral), or other infection that is uncontrolled or requires intravenous antimicrobials for management
   - History or presence of primary central nervous system (CNS) lymphoma, CNS disorders such as seizure disorder, cerebrovascular ischemic/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement
   - Uncontrolled, active inflammatory disorders
   - Active graft versus host disease (GVHD)

CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY FOR LEUKEMIA AND LYMPHOMA

Approval duration: One-time treatment infusion per lifetime for any CAR T-cell therapy treatment

Renewal Information: Continued therapy will not be authorized for any CAR T-cell therapy treatment

- Breyanzi (lisocabtagene maraleucel) for all other indications not previously listed is considered ***experimental or investigational*** and will not be covered when any **ONE** or more of the following criteria are met:

  1. Lack of final approval from the appropriate governmental regulatory bodies (e.g., Food and Drug Administration); or
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes; or
  3. Insufficient evidence to support improvement of the net health outcome; or
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives; or
  5. Insufficient evidence to support improvement outside the investigational setting.

  These indications include, *but are not limited to*:

  - Treatment with dosing, frequency or duration outside the FDA-approved dosing, frequency or duration.

KYMRIAH (tisagenlecleucel)

- **Criteria for therapy:** Kymriah (tisagenlecleucel) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

  2. Individual has a confirmed diagnosis of **ONE** of the following:

     - B-Cell precursor acute lymphoblastic leukemia (ALL) with morphologic bone marrow tumor involvement (> 5% lymphoblasts) that is refractory or in second or later relapse
     - Relapsed or refractory large B-Cell lymphoma after two or more lines of systemic therapy, including diffuse large B-Cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma
     - Relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy
     - Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

3. **For B-Cell precursor ALL indication**

   - Individual meets **ALL** of the following**:**

     a. Individual is 25 years of age or younger
     b. Individual has **ONE** of the following:

        - Second or later bone marrow relapse
        - Bone marrow relapse after allogeneic stem cell transplant
        - Refractory disease defined as failure to achieve complete response after induction chemotherapy

     c. Individual has confirmed CD19 positive disease
     d. For **Philadelphia chromosome positive (Ph+) ALL,** individual has had failure, intolerance or FDA label contraindication to TWO tyrosine kinase inhibitors (TKIs) (e.g., bosutinib, dasatinib, imatinib, nilotinib, and ponatinib)
     e. Individual does not have central nervous system acute lymphoblastic leukemia (i.e., white blood cell count ≥ cells/µL in cerebrospinal fluid with presence of lymphoblasts)
     f. Individual does not have Burkitt lymphoma/leukemia
     g. Individual does not have concomitant genetic syndrome associated with bone marrow failure with the exception of Down syndrome
     h. Performance rating scale of either Karnofsky (age ≥ 16 years) or Lansky (age < 16 years) performance status ≥ 50%
     i. Individual of child-bearing potential has a negative pregnancy test

4. **For B-Cell lymphoma indication**

   - Individual meets **ALL** of the following:

     a. Individual is 18 years of age or older
     b. The disease is relapsed or refractory after ≥ 2 prior chemotherapy regimens that included an anti-CD20 monoclonal antibody (e.g., obinutuzumab, ofatumumab, or rituximab) and at least one anthracycline (e.g., doxorubicin or pegylated liposomal doxorubicin) or anthracenedione-based regimen (e.g., mitoxantrone), unless contraindicated
     c. For DLBCL from transformed follicular lymphoma: individual has received prior chemotherapy for follicular lymphoma and subsequently has refractory disease after treatment for transformed DLBCL
     d. Individual of child-bearing potential has a negative pregnancy test
     e. Eastern Co-operative Oncology Group (ECOG) performance status of 0-1

5. **For follicular lymphoma indication**

   - Individual meets **ALL** of the following:

a. Individual is 18 years of age or older
b. Disease is classified as **ONE** of the following:

- Refractory or relapsed within 6 months after completion of two or more lines of systemic therapy including an anti-CD20 monoclonal antibody (e.g., obinutuzumab, ofatumumab, or rituximab) and at least one anthracycline (e.g., doxorubicin or pegylated liposomal doxorubicin)
- Relapsed during or within 6 months after completion of an anti-CD20 antibody (e.g., obinutuzumab, ofatumumab, or rituximab) maintenance therapy following at least TWO lines of therapy
- Relapsed after autologous hematopoietic stem cell transplant (HSCT)

c. Individual of child-bearing potential has a negative pregnancy test
d. Eastern Co-operative Oncology Group (ECOG) performance status of 0-1

6. Individual has absence of **ALL** of the following:

- Prior CAR T-cell therapy or any other gene therapy or is being considered for treatment with any other gene therapy
- Clinically significant active systemic fungal, bacterial, viral (hepatitis B, C, or other viral), or other infection that is uncontrolled or requires intravenous antimicrobials for management
- History or presence of primary central nervous system (CNS) lymphoma, CNS disorders such as seizure disorder, cerebrovascular ischemic/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement
- Uncontrolled, active inflammatory disorders
- Active graft versus host disease (GVHD)

Approval duration: One-time treatment infusion per lifetime for any CAR T-cell therapy treatment

Renewal Information: Continued therapy will not be authorized for any CAR T-cell therapy treatment

- Kymriah (tisagenlecleucel) for all other indications not previously listed is considered ***experimental or investigational*** and will not be covered when any **ONE** or more of the following criteria are met:

1. Lack of final approval from the appropriate governmental regulatory bodies (e.g., Food and Drug Administration); or
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes; or
3. Insufficient evidence to support improvement of the net health outcome; or
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives; or
5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, *but are not limited to:*

- Treatment with dosing, frequency or duration outside the FDA-approved dosing, frequency or duration.

TECARTUS (brexucabtagene autoleucel)

- **Criteria for therapy:** Tecartus (brexucabtagene autoleucel) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of **ONE** of the following:

   - B-cell precursor acute lymphoblastic leukemia (ALL) with morphologic bone marrow tumor involvement (≥ 5% lymphoblasts) that is **ONE** of the following:

     a. Primary refractory disease
     b. First relapse if remission is 12 months or less
     c. Relapsed or refractory disease after 2 or more lines of systemic therapy
     d. Relapsed or refractory disease after allogeneic stem cell transplant

   - Relapsed or refractory mantle cell lymphoma (MCL) only after chemoimmunotherapy and Bruton Tyrosine Kinase (BTK) inhibitor
   - Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

4. **For B-cell precursor ALL indication**

   - Individuals with Philadelphia chromosome positive (PH+) disease have relapsed or refractory disease despite treatment with tyrosine kinase inhibitors (TKIs) (e.g., bosutinib, dasatinib, imatinib, nilotinib, and ponatinib) unless has intolerance or FDA label contraindication to TKIs

5. **For mantle cell lymphoma indication**

   - Individual has received at least 2 to 5 prior regimens that must include:

     a. Anthracycline (e.g., doxorubicin or pegylated liposomal doxorubicin) or bendamustine containing chemotherapy

b. Anti-CD20 monoclonal antibody therapy (e.g., obinutuzumab, ofatumumab, or rituximab)
c. Bruton Tyrosine Kinase (BTK) inhibitor (e.g., acalabrutinib, ibrutinib, or zanubrutinib)

6. Individual meets **ALL** of the following:

- Eastern Co-operative Oncology Group (ECOG) performance status of 0-1
- Individual of child-bearing potential has a negative pregnancy test

7. Individual has absence of **ALL** of the following:

- Prior CAR T-cell therapy or any other gene therapy or is being considered for treatment with any other gene therapy
- Clinically significant active systemic fungal, bacterial, viral (hepatitis B, C, or other viral), or other infection that is uncontrolled or requires intravenous antimicrobials for management
- History or presence of CNS disorders such as seizure disorder, cerebrovascular ischemic/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement
- Uncontrolled, active inflammatory disorders
- Active graft versus host disease (GVHD)

Approval duration: One-time treatment infusion per lifetime for any CAR T-cell therapy treatment

Renewal Information: Continued therapy will not be authorized for any CAR T-cell therapy treatment

- Tecartus (brexucabtagene autoleucel) for all other indications not previously listed is considered ***experimental or investigational*** and will not be covered when any **ONE** or more of the following criteria are met:

1. Lack of final approval from the appropriate governmental regulatory bodies (e.g., Food and Drug Administration); or
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes; or
3. Insufficient evidence to support improvement of the net health outcome; or
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives; or
5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, *but are not limited to:*

- Treatment with dosing, frequency or duration outside the FDA-approved dosing, frequency or duration.

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YESCARTA (axicabtagene ciloleucel)

- **Criteria for therapy:** Yescarta (axicabtagene ciloleucel) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

  2. Individual is 18 years of age or older

  3. Individual has a confirmed diagnosis of **ONE** of the following:

     - Large B-cell lymphoma that is refractory to first line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy
     - Relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy
     - Relapsed or refractory B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
     - Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

  4. Individual meets **ALL** of the following:

     - Has received prior chemotherapy regimen that included an anti-CD20 monoclonal antibody, unless CD20 negative, (e.g., obinutuzumab, ofatumumab, or rituximab) and at least one anthracycline (e.g., doxorubicin or pegylated liposomal doxorubicin), unless contraindicated
     - Eastern Co-operative Oncology Group (ECOG) performance status of 0-1
     - Individual of child-bearing potential has a negative pregnancy test

  5. **For DLBCL transformed from follicular lymphoma (FL):** Individual has received prior chemotherapy for follicular lymphoma and subsequently has refractory disease after treatment for transformed DLBCL

  6. Individual has absence of **ALL** of the following:

     - Prior CAR T-cell therapy or any other gene therapy or is being considered for treatment with any other gene therapy
     - Clinically significant active systemic fungal, bacterial, viral (hepatitis B, C, or other viral), or other infection that is uncontrolled or requires intravenous antimicrobials for management
     - History or presence of primary central nervous system (CNS) lymphoma, CNS disorders such as seizure disorder, cerebrovascular ischemic/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement
     - Uncontrolled, active inflammatory disorders

- Active graft versus host disease (GVHD)

Approval duration: One-time treatment infusion per lifetime for any CAR T-cell therapy treatment

Renewal Information: Continued therapy will not be authorized for any CAR T-cell therapy treatment

- Yescarta (axicabtagene ciloleucel) for all other indications not previously listed is considered ***experimental or investigational*** and will not be covered when any **ONE** or more of the following criteria are met:

1. Lack of final approval from the appropriate governmental regulatory bodies (e.g., Food and Drug Administration); or
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes; or
3. Insufficient evidence to support improvement of the net health outcome; or
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives; or
5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, *but are not limited to:*

- Treatment with dosing, frequency or duration outside the FDA-approved dosing, frequency or duration.

Description:

Chimeric antigen receptor T (CART) cells are a form of genetically modified autologous immunotherapy that can be directed at B cell lymphoma. This customized treatment uses the individual's own T lymphocytes, which are genetically modified (transfected) with a gene that encodes a chimeric antigen receptor to direct the individual's T cells against the lymphoma cells. The T cells are genetically modified ex-vivo, expanded in a production facility, and then infused back into the individual as therapy.

Breyanzi (lisocabtagene maraleucel), Kymriah (tisagenlecleucel), Tecartus (brexucabtagene autoleucel), and Yescarta (axicabtagene ciloleucel) are CD19-directed genetically modified autologous T cell immunotherapy, also known as chimeric antigen receptor T cell therapy (CART), that binds to CD19-expressing cancer cells and normal B cells.

Breyanzi is indicated for the treatment of adult patients with large B-cell lymphoma, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including BLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B in individuals 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 (HSCT) due to comorbidities or age; or relapsed or refractory disease after two or more lines of systemic therapy; adult patients with relapsed or refractory mantle cell lymphoma (MCL) who have received at least 2 prior lines of systemic therapy, including a Bruton tyrosine kinase (BTK) inhibitor; adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have received at least 2 prior lines of therapy, including a BTK inhibitor and a B-cell lymphoma 2 (BCL-2) inhibitor; and adult patients with relapsed or refractory follicular lymphoma (FL) who have received 2 or more prior lines of systemic therapy. The CLL or SLL indication and the FL indication are approved under accelerated approval based on response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials. Breyanzi is not indicated for the treatment of patients with primary central nervous system lymphoma.

Kymriah is indicated for the treatment of pediatric and young adult patients with relapsed or refractory B-cell Acute Lymphoblastic Leukemia (ALL) in patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse; for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma; and for adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy. The FL indication is approved under accelerated approval based on response rate and duration of response. Continued approval for FL indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). Kymriah is not indicated for treatment of patients with primary central nervous system lymphoma.

Tecartus is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL). This indication is approved under accelerated approval based on overall response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. Tecartus is also indicated for adult patients with relapsed or refractory B-cell precursor ALL.

Yescarta is indicated for the treatment of adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy; for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two 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; and for adult patients with relapsed or refractory FL after two or more lines of systemic therapy. FL 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 trials. Yescarta is not indicated for the treatment of patients with primary central nervous system lymphoma.

Breyanzi (lisocabtagene maraleucel), Kymriah (tisagenlecleucel), Tecartus (brexucabtagene autoleucel), and Yescarta (axicabtagene ciloleucel) carry Boxed Warnings for Cytokine Release Syndrome (CRS), neurologic toxicities including fatal or life-threatening reactions that occurred in patients receiving CAR-T therapy, and T cell malignancies that have occurred following CAR-T therapies. CAR-T therapy should

not be administered to individuals with active infection nor inflammatory disorders. CAR-T therapies are available through Risk Evaluation and Mitigation Strategy (REMS) programs.

Definitions:

Adult: Age 18 years and older

Complete Response (CR): The disappearance of all signs of cancer as a result of treatment; also called complete remission; does not indicate the cancer has been cured

Minimal residual disease (MRD): Presence of disease in cases deemed to be in complete remission by conventional pathologic analysis

Relapsed disease for ALL: Reappearance of leukemic cells in the bone marrow or peripheral blood after the attainment of a complete remission (CR) with chemotherapy and/or allogeneic cell transplant

Refractory (resistant) disease for ALL: Patients who fail to obtain CR 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)

Relapse or refractory disease for B-cell lymphoma: Progression after 2 or more lines of systemic therapy (which may or may not include therapy support by autologous cell transplant)

Risk Evaluation and Mitigation Strategy (REMS) Program:
Use of Yescarta (axicabtagene ciloleucel), Kymriah (tisagenlecleucel), Tecartus (brexucabtagene autoleucel), and Breyanzi (lisocabtagene maraleucel) are subject to a Risk Evaluation and Mitigation Strategies (REMS) program that requires provider, patient, and dispensing pharmacy be enrolled into the program. Only providers and Pharmacies enrolled into the REMS may prescribe and dispense the drug, respectively, to individuals who are also in the program. A REMS program attempts to manage known or potentially serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) for some drugs to ensure that the benefits of a drug outweigh its risks.

Because of risk of CRS and neurologic toxicities, Yescarta (axicabtagene ciloleucel), Kymriah (tisagenlecleucel), Tecartus (brexucabtagene autoleucel), and Breyanzi (lisocabtagene maraleucel) are available through a restricted REMS program.

Requirements of the Yescarta (axicabtagene ciloleucel), Kymriah (tisagenlecleucel), Tecartus (brexucabtagene autoleucel), and Breyanzi (lisocabtagene maraleucel) REMS Program include the following:

- Healthcare facilities that dispense and administer must be enrolled and comply with the REMS requirements.

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- Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of two doses of tocilizumab are available for each patient for administration within 2 hours after CAR-T infusion, if needed for treatment of Cytokine Release Syndrome (CRS)
- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer CAR-T are trained about the management of CRS and neurological toxicities

Anthracycline and Anti-CD 20 Monoclonal Antibody Agents Table:

Anthracycline Agents	Anti-CD 20 Monoclonal Antibody Agents	Alkylating Agents
Adriamycin (doxorubicin hydrochloride, conventional)	Arzerra (ofatumumab)	Bendamustine
Doxil or Lipodox 50 (doxorubicin hydrochloride, liposomal (pegylated liposomal doxorubicin))	Gazyva (obinutuzumab)	Carboplatin
Mitoxantrone – anthracenedione, related to anthracyclines	Rituxan (rituximab) or biosimilars Riabni, Ruxience, Truxima	Carmustine
	Rituxan hycela (rituximab/hyaluronidase)	Chlorambucil
	Zevalin Y-90 (ibritumomab tiuxetan)	Cisplatin
		Cyclophosphamide
		Ifosfamide
		Lomustine
		Melphalan
		Oxaliplatin
		Procarbazine
		Decarbazine

B-Cell Lymphoma 2 (BCL-2) inhibitor:

- Venclexta (venetoclax)

Tyrosine Kinase Inhibitors:

- Bosulif (bosutinib)
- Sprycel (dasatinib)
- Gleevec (imatinib) or imatinib generic
- Tasigna (nilotinib)
- Iclusig (ponatinib)

Bruton tyrosine kinase (BTK) inhibitor:

- Calquence (acalabrutinib)
- Imbruvica (ibrutinib)
- Brukinsa (zanubrutinib)

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Central Nervous System (CNS) Disease for B-cell Acute Lymphoblastic Leukemia Table:

CNS 1	Absence of lymphoblasts in the cerebrospinal fluid (CSF), regardless of the white blood cell (WBC) count
CNS 2	WBC count of less than 5 leukocytes/µL in the CSF with the presence of blasts
CNS 3	WBC count of 5 leukocytes/µL or more with the presence of blasts and/or clinical signs of CNS leukemia (e.g., facial nerve palsy, brain/eye involvement, hypothalamic syndrome

ECOG Performance Status Table:

Eastern Co-operative Oncology Group (ECOG) Performance Status	
Grade	ECOG description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982	

Karnofsky Scale:

Score	Description	
100	Normal, no complaints, no evidence of disease	Able to carry on normal activity and to work No special care needed
90	Able to carry on normal activity, minor signs, or symptoms of disease	
80	Normal activity with effort, some signs or symptoms of disease	
70	Cares for self, unable to carry on normal activity or do active work	Unable to work but able to live at home and care for most personal needs Various degrees of assistance may be needed
60	Requires occasional assistance, but is able to care for most of his/her needs	
50	Requires considerable assistance and frequent medical care	
40	Disabled, requires special care and assistance	Unable to care for self Requires equivalent of institutional or hospital care
30	Severely disabled, hospitalization indicated, but death not imminent	
20	Very sick, hospitalization indicated, but death not imminent	
10	Moribund, fatal process progressing rapidly	
0	Dead	

Lansky Scale:

Score	Description
100	Fully active, normal
90	Minor restrictions in physical strenuous activity
80	Active, but tires more quickly

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70	Both greater restriction of, and less time spent in, play activity
60	Up and around, but minimal active play; keeps busy with quieter activities
50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities
40	Mostly in bed, participates in quiet activities
30	In bed, needs assistance even for quiet play
20	Often sleeping, play entirely limited to very passive activities
10	No play, does not get out of bed
0	Dead

History:	**Date:**	**Activity:**
Pharmacy and Therapeutics Committee	08/15/24	Review with revisions: criteria
Pharmacy and Therapeutics Committee	08/17/23	Reviewed and revised criteria
Pharmacy and Therapeutics Committee	08/18/22	Reviewed and revised criteria, codes
Medical Policy Panel	09/28/21	Approved guideline
Clinical Pharmacist	09/16/21	Development

Coding:

CPT: 0537T, 0538T, 0539T, 0540T
HCPCS: Q2041, Q2042, Q2053, Q2054

CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY FOR LEUKEMIA AND LYMPHOMA

Resources:

Literature reviewed 08/15/24. We do not include marketing materials, poster boards and non-published literature in our review.

1. Breyanzi (lisocabtagene maraleucel). Prescribing information. Juno Therapeutics Inc.; May 2024 at DailyMed http://dailymed.nlm.nih.gov. Accessed July 1, 2024.

2. Freedman AS, Friedberg JW. Treatment of relapsed or refractory follicular lymphoma. In: UpToDate, Lister A, Connor RF (Eds). UpToDate, Waltham, MA.: Available at http://uptodate.com. Topic last updated May 24, 2024. Accessed July 1, 2024.

3. Freedman AS, Friedberg JW. Treatment of relapsed or refractory mantle cell lymphoma. In: UpToDate, Lister A, Rosmarin AG (Eds). UpToDate, Waltham, MA.: Available at http://uptodate.com. Topic last updated August 31, 2023. Accessed July 1, 2024.

4. Friedberg JW. Diffuse large B cell lymphoma (DLBCL): Suspected first relapse or refractory disease in patients who are medically fit. In: UpToDate, Negrin RS, LaCasce AS, Rosmarin AG (Eds). UpToDate, Waltham, MA.: Available at http://uptodate.com. Topic last updated June 25, 2024. Accessed July 1, 2024.

5. Horton TM, McNeer JL. Treatment of acute lymphoblastic leukemia/lymphoma in children and adolescents. In: UpToDate, Newburger P, Rosmarin AG (Eds). UpToDate, Waltham, MA.: Available at http://uptodate.com. Topic last updated November 29, 2022. Accessed July 1, 2024.

6. Institute for Clinical and Economic Review (ICER), 2018. Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value Final Evidence Report. 03/23/2017. https://icer-review.org/wp-content/uploads/2017/07/ICER_CAR_T_Final_Evidence_Report_032318.pdf.

7. Kymriah (tisagenlecleucel). Prescribing information. Novartis Pharmaceuticals Corporation; June 2024 at DailyMed http://dailymed.nlm.nih.gov. Accessed July 1, 2024.

8. Larson RA. Treatment of relapsed or refractory acute lymphoblastic leukemia in adults. In: UpToDate, Lowenberg B, Rosmarin AG (Eds). UpToDate, Waltham, MA.: Available at http://uptodate.com. Topic last updated June 3, 2022. Accessed July 1, 2024.

9. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Acute Lymphoblastic Leukemia Version 1.2023. Updated 05/31/2023; https://www.nccn.org. Accessed July 1, 2024.

10. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): B-Cell Lymphomas Version 2.2024. Updated 04/30/2024; https://www.nccn.org. Accessed July 1, 2024.

11 National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Version 3/2024. Updated 03/36/2024; https://www.nccn.org. Accessed July 1, 2024.

12. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Pediatric Acute Lymphoblastic Leukemia Version 5.2024. Updated 04/03/2024; https://www.nccn.org. Accessed July 1, 2024.

13. Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions. https://www.azleg.gov/ars/20/00826.htm.

14. Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions. https://www.azleg.gov/ars/20/01057.htm.

15. Rai KR, Stilgenbauer. Treatment of relapsed or refractory chronic lymphocytic leukemia. In: UpToDate, Woyach J, Connor RF (Eds). UpToDate, Waltham, MA.: Available at http://uptodate.com. Topic last updated April 12, 2024. Accessed July 1, 2024.

16. Tecartus (brexucabtagene autoleucel). Prescribing information. Kite Pharma, Inc.; June 2024 at DailyMed http://dailymed.nlm.nih.gov. Accessed July 1, 2024.

17. Yescarta (axicabtagene ciloleucel). Prescribing information. Kite Pharma, Inc.; June 2024 at DailyMed http://dailymed.nlm.nih.gov. Accessed July 1, 2024.

EVIDENCE-BASED CRITERIA	**ORIGINAL EFFECTIVE DATE: 09/28/21**
SECTION: SPECIALTY MEDICAL DRUGS	**LAST REVIEW DATE: 08/15/24**
	CURRENT EFFECTIVE DATE: 08/15/24
	LAST CRITERIA REVISION DATE: 08/15/24
NEXT REVIEW DATE: 3RD QTR 2025	**ARCHIVE DATE:**

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