

Corporate Medical Policy

CAR-T Therapy

File Name:	car_t_therapy
Origination:	9/2017
Last CAP Review:	8/2018
Next CAP Review:	8/2019
Last Review:	8/2018

Description of Procedure or Service

Engineered T cell–based antitumor immunotherapy uses gene transfer of tumor antigen-specific T-cell receptors (TCR) or synthetic chimeric antigen receptors (CAR-T). CAR-T cells are prepared from the patient’s peripheral blood mononuclear cells, which are obtained via a standard leukapheresis procedure. The blood is sent to the manufacturer where the mononuclear cells are enriched for T cells. The T cells are expanded in cell culture, washed, and formulated into a suspension, which then is cryopreserved. This process may take several weeks. The product is then infused into the patient. This technique has shown very encouraging results in clinical trials for treatment of types of leukemias and lymphomas. However, CAR-T cells can persist more than 6 years in patients and can lead to severe adverse events shortly after infusion as well as at later times.

Cytokine-release syndrome (CRS) and other toxicities pose significant risks for patients. Providers develop toxicity management plans for patients undergoing CAR-T therapy. There are on-going clinical studies to determine the effectiveness of various toxicity management plans.

KYMRIAH™ (tisagenlecleucel) is a CD19-directed genetically modified autologous T cell immunotherapy used in patients up to 25 years old who have acute lymphoblastic leukemia (ALL) that is either relapsing or refractory. In addition, tisagenlecleucel is indicated for the treatment of adult patients with 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.

YESCARTA® (axicabtagene ciloleucel) is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with 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, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

BCBSNC will provide coverage for CAR-T Therapy when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit

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design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When CAR-T Therapy is covered

Tisagenlecleucel (Kymriah) is considered medically necessary for the treatment of patients with refractory or second relapse B-cell precursor acute lymphoblastic leukemia (ALL) when the following criteria are met:

1. The patient has been diagnosed with relapsed/refractory B-cell precursor acute lymphoblastic leukemia (ALL); **AND**
2. The patient is 25 years of age or younger; **AND**
3. The patient has a confirmed CD19 tumor expression; **AND**
4. The patient has not previously been treated with gene therapy or Kymriah; **AND**
5. If the patient has Philadelphia Chromosome positive (Ph+) ALL, they have tried and failed, is intolerant to, or has a contraindication to at least 2 tyrosine kinase inhibitors (TKI); **AND**
6. The patient will not be treated with more than 2.5×10^8 CAR-positive viable T cells; **AND**
7. If the patient is 50kg or less in weight, they will receive weight-based dosing at 0.2 to 5.0×10^6 CAR-positive viable T cells per kg of body weight; **AND**
8. The patient has received or will receive lymphodepleting chemotherapy [Fludarabine (30 mg/m² intravenous daily for 4 days) and cyclophosphamide (500 mg/m² intravenous daily for 2 days starting with the first dose of fludarabine)] within two weeks preceding Kymriah infusion; **AND**
9. The patient has been treated with 2 cycles of standard chemotherapy without a complete response or achieved a complete response and experienced multiple relapses following standard chemotherapy (at least 2 cycles); **AND**
10. The patient does not have active central nervous system (CNS) 3 acute lymphoblastic leukemia.

Tisagenlecleucel (Kymriah) is considered medically necessary for the treatment of patients with relapsed or refractory B-cell lymphoma when the following criteria are met:

1. The patient has been diagnosed with relapsed/refractory B-cell lymphoma including any of the following:
 - a. Diffuse large B-cell lymphoma (DLBCL) not otherwise specified; **OR**
 - b. High grade B-cell lymphoma; **OR**
 - c. Diffuse large B-cell lymphoma (DLBCL) arising from follicular lymphoma; **AND**
2. The patient is 18 years of age or older; **AND**
3. The patient has not previously been treated with gene therapy or Kymriah; **AND**
4. The patient has experienced disease progression following a trial of two or more lines of systemic therapy; **AND**
5. Previous therapy included anthracycline chemotherapy agent and an anti-CD20 antibody; **AND**

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6. The patient will be treated within a dosage range of 0.6 to 6.0 x 10⁸ CAR-positive viable T cells; **AND**
7. The patient has received or will receive lymphodepleting chemotherapy [Fludarabine (25 mg/m² intravenous daily for 3 days) and cyclophosphamide (250 mg/m² intravenous daily for 3 days starting with the first dose of fludarabine), or alternate therapy with bendamustine 90 mg/m² intravenous daily for 2 days for patients unable to receive cyclophosphamide] within two weeks preceding Kymriah infusion, **OR** the patient is unable to receive lymphodepleting chemotherapy if WBC count is less than or equal to 1x10⁹/L within one week prior to Kymriah infusion; **AND**
8. The patient does not have primary central nervous system lymphoma; **AND**
9. The patient does not have human immunodeficiency virus (HIV), active Hepatitis B or C, active uncontrolled infection and any autoimmune disease requiring immune suppression.

Axicabtagene Ciloleucel (Yescarta) is considered medically necessary when the following criteria are met:

1. The patient has been diagnosed with relapsed/refractory B-cell lymphoma including any of the following:
 - a. Diffuse large B-cell lymphoma (DLBCL) not otherwise specified; **OR**
 - b. Primary mediastinal large B-cell lymphoma; **OR**
 - c. High grade B-cell lymphoma; **OR**
 - d. Diffuse large B-cell lymphoma (DLBCL) arising from follicular lymphoma; **AND**
2. The patient is 18 years of age or older; **AND**
3. The patient has not previously been treated with gene therapy or Yescarta; **AND**
4. The patient has experienced disease progression following a trial of two or more lines of systemic therapy; **AND**
5. Previous therapy included anthracycline chemotherapy agent and an anti-CD20 antibody; **AND**
6. The patient will not be treated with more than 2 x 10⁸ CAR-positive viable T cells; **AND**
7. If the patient is under 100kg in weight, they will receive weight-based dosing 2 x 10⁶ CAR-positive viable T cells; **AND**
8. The patient has received or will receive lymphodepleting cyclophosphamide 500mg/m² intravenously and fludarabine 30 mg/m² intravenously on the fifth, fourth, and third day before infusion of Yescarta; **AND**
9. The patient does not have primary central nervous system (CNS) lymphoma; **AND**
10. The patient does not have human immunodeficiency virus (HIV), active Hepatitis B or C, active uncontrolled infection and any autoimmune disease requiring immune suppression.

When CAR-T Therapy is not covered

Tisagenlecleucel (Kymriah) is considered investigational for all other indications not listed above.

Axicabtagene Ciloleucel (Yescarta) is considered investigational for all other indications not listed above.

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Policy Guidelines

Tisagenlecleucel (Kymriah) is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. Kymriah is also indicated for the treatment of adult patients with 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.

Axicabtagene ciloleucel (Yescarta) is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with 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, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Research on CAR-T cell therapy is ongoing. Novartis manufactures tisagenlecleucel (Kymriah) and it was FDA approved in August 2017. Kite Pharmaceuticals manufactures axicabtagene ciloleucel (Yescarta), which received FDA approval in October 2017.

There are warnings published by the FDA regarding administration of Kymriah and Yescarta:

Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving Kymriah or Yescarta. Do not administer Kymriah or Yescarta to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab.

Neurological toxicities, which may be severe or life-threatening, can occur following treatment with Kymriah or Yescarta, including concurrently with CRS. Monitor for neurological events after treatment with Kymriah or Yescarta. Provide supportive care as needed.

Kymriah and Yescarta are available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIAH REMS and YESCARTA REMS, respectively.

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

- 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/ μ L in the CSF with the presence of blasts
- CNS 3: WBC count of 5 leukocytes/ μ L or more with the presence of blasts and/or clinical signs of CNS leukemia (e.g., facial nerve palsy, brain/eye involvement, hypothalamic syndrome)

Longitudinal follow up of individual member's treatment outcomes may be needed to verify the effectiveness of therapy and the necessity for additional treatment. The various methods used to achieve this may include case management services, clinical registry data collection, evaluation of clinical trial eligibility, and/or requests for medical records.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 0537T, 0538T, 0539T, 0540T, Q2041, Q2042

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Q2041 – Axicabtagene Ciloleucel, up to 200 Million Autologous Anti-CD19 CAR Positive Viable T Cells, Including Leukapheresis And Dose Preparation Procedures, Per Therapeutic Dose

Q2042 – Tisagenlecleucel, up to 600 Million CAR Positive Viable T Cells, Including Leukapheresis And Dose Preparation Procedures, Per Therapeutic Dose

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

Hartmann J, Schüler-Lenz M, Bondanza A, Buchholz CJ. Clinical development of CAR T cells- challenges and opportunities in translating innovative treatment concepts. EMBO Mol Med. 2017 August 1. <http://embomolmed.embopress.org/content/early/2017/07/31/emmm.201607485.long>

<https://www.cancer.gov/about-cancer/treatment/research/car-t-cells>

Kymriah (tisagenlecleucel). Highlights of prescribing information. August 2017. Available at: <https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/kymriah.pdf>

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Yescarta (axicabtagene ciloleucel). Highlights of prescribing information. Available at: <https://www.yescarta.com/wp-content/uploads/yescarta-pi.pdf>

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BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.01, 4/12/2018

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Guidelines for Acute Lymphoblastic Leukemia. Version 1.2018. Fort Washington, PA: NCCN, 3/12/18. Available at: https://www.nccn.org/professionals/physician_gls/pdf/all.pdf. Accessed May 2018.

Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med. 2018;378(5):439-448. [PubMed 29385370]. Available at: <https://www.nejm.org/doi/full/10.1056/NEJMoa1709866>. Accessed May 2018.

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Kymriah (tisagenlecleucel). Highlights of prescribing information. May 2018. Available at: <https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/kymriah.pdf>. Accessed June 2018.

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Specialty Matched Consultant Advisory Panel 8/2018

Policy Implementation/Update Information

- 9/29/17 New policy developed. CAR-T Therapy is considered medically necessary for the treatment of patients with refractory or second relapse B-cell precursor acute lymphoblastic leukemia (ALL) when the medical criteria and guidelines above are met. References added. (lpr)
- 11/28/17 Added Axicabtagene Ciloleucef (Yescarta) criteria as a covered indication. Added CPT codes Q2040 and 36511 to the Billing/Coding section. Reference added. (lpr)
- 12/15/17 Under “When Covered” section, corrected dosage under Yescarta from 2.5 to 2 in #6 and #7. No change to policy intent. Codes Q2040 and 36511 are effective 1/1/2018. (lpr)
- 3/29/18 Added CPT Q2041 and deleted CPT 36511 in Billing/Coding section for 4/1/2018 code update. (lpr)
- 4/27/18 Removed the following criterion from “When Covered” section for both Kymriah and Yescarta coverage: “The prescriber will submit documentation of response within 3 months following therapy as a follow up to the prior approval request.” Added the following to “Policy Guidelines” section: “Longitudinal follow up of individual member’s treatment outcomes may be needed to verify effectiveness of therapy and the necessity for additional treatment. The various methods used to achieve this may include case management services, clinical registry data collection, evaluation of clinical trial eligibility, and/or requests for medical records.” Other minor updates made to organization and wording of “Policy Guidelines” section for clarity. Removed codes C9399 and J3590 from Billing/Coding section, and added code descriptions for codes Q2040 and Q2041. References added. Medical Director review 4/2018. (krc)
- 5/25/18 Updated “When Covered” section for Kymriah to include criterion “The patient does not have active central nervous system (CNS) 3 acute lymphoblastic leukemia.” Added definitions of CNS disease for B-cell acute lymphoblastic leukemia in Policy Guidelines section. References added. Medical Director review 5/2018. (krc)
- 6/29/18 Updated “When Covered” section for Kymriah to include medically necessary criteria for newly approved indication for diffuse large B-cell lymphoma (DLBCL). “Description” and “Policy Guidelines” sections updated to reflect additional DLBCL indication for Kymriah. Reference added. (krc)
- 10/12/18 Specialty Matched Consultant Advisory Panel review 8/22/2018. No change to policy statement. (krc)
- 12/31/18 Added HCPCS code Q2042 and associated description to Billing/Coding section, deleted code Q2040, and revised description of code Q2041, effective 1/1/19. (krc)
- 1/29/19 Added codes 0537T, 0538T, 0539T, and 0540T to Billing/Coding section effective 1/1/19. (krc)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.