Blue Cross Blue Shield Blue Care Network of Michigan

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Effective Date: 06/06/2024

Kymriah™ (tisagenlecleucel)

HCPCS: Q2042

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

A. Coverage of the requested drug is provided when all the following are met:
   a. Prescribed by or in consultation with an oncologist
   b. Diagnosis of pediatric and young adult with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory[a] or in second or later relapse[b]:
      i. FDA approved age
      ii. Primary refractory as defined by not achieving a complete response after 2 cycles of a standard chemotherapy regimen or chemorefractory as defined by not achieving a complete response after 1 cycle of standard chemotherapy for relapsed leukemia
      iii. Patients with Philadelphia chromosome positive (Ph+) ALL are eligible if they are intolerant to or have failed 2 lines of tyrosine kinase inhibitor therapy (TKI), or if TKI therapy is contraindicated
      iv. Any bone marrow (BM) relapse after allogenic SCT
      v. Patient must meet all of the following:
         1. No Burkitt's lymphoma
         2. No HIV infection; hepatitis B or C virus infection permitted only if viral load undetectable
         3. No infection that is uncontrolled or requires IV or long-term oral antimicrobial therapy
         4. No grade 2 to 4 graft-versus-host disease
         5. No concomitant genetic syndrome with the exception of Down's syndrome
         6. Must not have received allogeneic cellular therapy, such as donor lymphocyte infusion within 6 weeks prior to tisagenlecleucel infusion
         7. No myocardial infarction, cardiac angioplasty or stenting, unstable angina, or New York Heart Association Class II or greater congestive heart failure events within 6 months
         8. No thromboembolic events within 6 months
         9. No pulmonary disease requiring oxygen dependence or pulmonary disease such as idiopathic pulmonary fibrosis, organizing pneumonia (eg, bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis per chest computed tomography (CT) scan at screening
         10. No clinically significant CNS pathology such as epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis

c. Treatment of adult patients with relapsed or refractory (r/r) 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:
    i. FDA approved age
    ii. Received ≥ 2 lines of chemotherapy, including rituximab and anthracycline
    OR
    iii. Relapsed following autologous hematopoietic stem cell transplantation (HSCT)
    iv. Patient must meet all of the following:
        1. No known active central nervous system malignancy
        2. No prior allogenic HSCT
        3. ECOG performance status 0 - 2
        4. Creatinine clearance greater than 30 mL/min
        5. Alanine aminotransferase less than 5 times normal
        6. Cardiac ejection fraction greater than 40%
        7. Absolute lymphocyte concentration greater than 300/µL
        8. No HIV infection; hepatitis B or C virus infection permitted only if viral load undetectable
        9. No active infection including hepatitis B, hepatitis C, HIV, or systemic fungal, bacterial, or viral infectionInfection that is uncontrolled or requires IV or long-term oral antimicrobial therapy
        10. No myocardial infarction, cardiac angioplasty or stenting, unstable angina, or New York Heart Association Class II or greater congestive heart failure events within 6 months
        11. No thromboembolic events within 6 months
        12. No pulmonary disease requiring oxygen dependence or pulmonary disease such as idiopathic pulmonary fibrosis, organizing pneumonia (eg, bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis per chest computed tomography (CT) scan at screening
        13. No clinically significant CNS pathology such as epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis
d. Treatment of adult patients with relapsed or refractory follicular lymphoma (FL)
    i. Subjects must have received at least 2 prior lines of therapy
    ii. Must have measurable disease
    iii. Patient must meet all of the following:
        1. No prior allogeneic HSCT
        2. No known active central nervous system malignancy
        3. ECOG performance status 0 - 2
        4. No transformed FL
        5. No histological grade 3b FL
        6. Creatinine clearance greater than 30 mL/min
        7. Hepatic transaminases less than 5 times the upper limit of normal
        8. Cardiac ejection fraction greater than 40%
        9. No HIV infection; hepatitis B or C virus infection permitted only if viral load undetectable
        10. No active infection including hepatitis B, hepatitis C, HIV, or systemic fungal, bacterial, or viral infectionInfection that is uncontrolled or requires IV or long-term oral antimicrobial therapy
        11. No myocardial infarction, cardiac angioplasty or stenting, unstable angina, or New York Heart Association Class II or greater congestive heart failure events within 6 months
        12. No thromboembolic events within 6 months
        13. No pulmonary disease requiring oxygen dependence or pulmonary disease such as idiopathic pulmonary fibrosis, organizing pneumonia (eg, bronchiolitis obliterans), drug-

induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis per chest computed tomography (CT) scan at screening

14. No clinically significant CNS pathology such as epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis

e. Have not received prior treatment with any CAR-T therapy despite indication or any other genetically-modified T-cell therapy or are being considered for treatment with any other genetically-modified T-cell therapy
f. Only to be administered at certified bone marrow/stem cell transplant centers
g. Trial and failure, intolerance, or a contraindication to the preferred products as listed in the BCBSM/BCN utilization management medical drug list
h. The requesting physician attests to providing clinical outcome information within the Audaire Health™ provider portal as requested by BCBSM
i. If new diagnoses are FDA approved, coverage will be determined based on the FDA approved indication on a case by case basis until fully evaluated by the BCBSM Pharmacy and Therapeutics Committee

B. Quantity Limitations, Authorization Period and Renewal Criteria
   a. Quantity Limits: Align with FDA recommended dosing
   b. Authorization Period: 3 months with the allowance of only one dose per lifetime
   c. Renewal Criteria: Not applicable as no further authorization will be provided

[a] Refractory (resistant) disease is defined as those patients who fail to obtain complete response with induction therapy, ie, failure to eradicate all detectable leukemia cells (<5% blasts) from the bone marrow and blood with subsequent restoration of normal hematopoiesis (>25% marrow cellularity and normal peripheral blood counts).

[b] 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 stem cell transplant

***Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Background Information:

- CAR-T therapy is a type of treatment the utilizes the body's own immune system to fight cancer. T-cells are collected from the patient via apheresis and are genetically engineered in the laboratory to produce chimeric antigen receptors on the cell surface, allowing the T-cells to recognize an antigen on target cancer cells. Once the tumor cells are identified, they are attacked and killed by the CAR-T therapy.

- CAR-T therapy has not been studied when given following prior treatment with any CAR-T therapy or following any other genetically-modified T-cell therapy.

- Due to the risk of cytokine release syndrome and neurological toxicities, CAR-T therapies are only allowed to be given at treatment centers certified by their REMS programs. CAR-T REMS programs require certified hospitals and their clinics to have on-site, immediate access to tocilizumab and an understanding of how to manage the risks of the associated CAR-T side effects.

- Kymriah is indicated for patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse. It is also approved for use in 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. It is not indicated for treatment of patients with primary central nervous system lymphoma.

- Safety and efficacy was established in two studies. The first was the ELIANA trial, an open-label, multicenter single-arm study of 107 pediatric and young adult patients with relapsed/refractory B-cell precursor ALL. All patients were screened, 88 were enrolled in the study, 68 were treated with CAR-T, and 63 were evaluable for efficacy. Nine percent of the enrolled subjects did not receive the product due to manufacturing failure. Treatment consisted of lymphodepleting chemotherapy (fludarabine 30 mg/m2 daily for 4 days and cyclophosphamide 500 mg/m2 daily for 2 days) followed by a single dose of Kymriah. Tumors must have had CD19 expressing tumor cells. Patients were included if they were primary refractory defined as not achieving a complete response after 2 cycles of a standard chemotherapy regimen or chemorefractory as defined by not achieving a complete response after 1 cycle of standard chemotherapy for relapsed leukemia; has Philadelphia chromosome positive (Ph+) ALL and were intolerant to or failed 2 lines of tyrosine kinase inhibitor therapy (TKI) or if TKI therapy was contraindicated; they were ineligible for allogeneic stem cell transplant (SCT); or had any bone marrow (BM) relapse after allogenic SCT. Patients were excluded if they had Burkitt's lymphoma, active hepatitis B or C, any uncontrolled infection, grade 2 to 4 graft-versus-host disease, concomitant genetic syndrome with the exception of Down's syndrome, or if they have received allogeneic cellular therapy, such as donor lymphocyte infusion within 6 weeks prior to Kymriah infusion. Efficacy was based on complete remission (CR) within 3 months after infusion, the duration of CR, and proportion of patients with CR and minimal residual disease (MRD) < 0.01% by flow cytometry (MRD-negative). Among the 63 infused patients, 52 (83%) achieved CR/CRi, all of which were MRD-negative. With a median follow-up of 4.8 months from response, the median duration of CR/CRi was not reached (range: 1.2 to 14.1+ months). Median time to onset of CR/CRi was 29 days with onset of CR/CRi between 26 and 31 days for 50/52 (96%) responders. The stem cell transplantation rate among those who achieved CR/CRi was 12% (6/52).

- Efficacy was also established in the JULIET trial, an open-label, multicenter, single-arm trial of 160 adult patients with relapsed or refractory DLBCL, who received ≥ 2 lines of chemotherapy, including rituximab and anthracycline, or relapsed following autologous hematopoietic stem cell transplantation (HSCT). Of the160 patients enrolled, 106 patients received Kymriah. Eleven patients enrolled did not receive Kymriah due to manufacturing failure and 38 other patients did not receive Kymriah due to death (n = 16), physician decision (n = 16), or adverse events (n = 3). Patients with active central nervous system malignancy, prior allogenic HSCT, an ECOG performance status ≥ 2, a creatinine clearance < 60, alanine aminotransferase > 5 times normal, cardiac ejection fraction < 45%, or absolute lymphocyte concentration less than 300/µL were excluded from the study. The primary endpoints were complete response (CR) rate and duration of response (DOR). The median time to first response was 0.9 months (range: 0.7 to 3.3 months). The median duration of response was not reached. Response durations were longer in patients who achieved CR as compared to patients with a best response of partial response (PR). Of the 22 patients who experienced a CR, 9 achieved this status by 1 month, 12 more by month 3, and the last by month 6 after Kymriah infusion.

- Efficacy and safety were established for follicular lymphoma in the ELARA trial, a phase II, single-arm, multicenter, open-label trial of 94 adult patients with relapsed/refractory follicular lymphoma after at least two prior therapies. Patients were excluded from the study if they had active central nervous system malignancy, prior allogenic HSCT, an ECOG performance status ≥ 2, transformed FL, or histological grade 3b FL. To be included, patients had to have measurable disease. The primary endpoint was complete response rate. The CR rate was 69% (95% CI, 60-78). Overall response rate (ORR) was 86% (95% CI, 78-92) with a 12-month progression-free survival (PFS) of 67% (95% CI, 56-76) and nine-month DOR was 76% (95% CI, 65-84). For patients who had a complete response, 12-month PFS was 86% (95% CI, 74-92) and the estimated DOR rate was 87% (95% CI, 75-93).

- Disease should be measured/staged with PET-CT. Focal uptake in nodal and extranodal sites is considered involvement with lymphoma, including spleen, liver, bone, thyroid, and so on. A measurable node must have a longest diameter (LDi) greater than 1.5 cm. A measurable extranodal lesion should have an LDi greater than 1.0 cm.

All other lesions (including nodal, extranodal, and assessable disease) should be followed as nonmeasured disease (eg, cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites).

- While use of Kymriah has not been established in patients with a creatinine clearance of less than 60 mL/minute, other CAR-T therapies have been studied in subjects with a creatinine clearance of 30 mL/minute. The National Institute of Health/National Cancer Institute Common Terminology Criteria of Adverse Events (CTCAE) classify grade 2 chronic kidney disease as a creatinine clearance of 30 – 59 mL/minute. As the classification system uses 30 mL/minute as a cutoff for grade 2 disease and data from other CAR-T therapies support their use in these patients, Kymriah should be able to be tolerated in this population. As there is no data to support administration of CAR-T at levels lower than 30 ml/minute, therapy should not be given in patients not meeting the 30 mL/minute threshold.

- The CTCAE recommendations set the grade 2 cutoff for left ventricular ejection fraction (LVEF) at 40%. While Kymriah has only been studied in patients with a LVEF greater than or equal to 45%, there is data from other CAR-T therapies to support use in those with a LVEF of 40% of greater. Therefore, Kymriah should be tolerated in these patients as well. There is no data supporting use at LVEF levels less than 40%.

- The Audaire Health™ platform is a provider portal that is used to capture clinical outcome information for patients on select high-cost treatments, such as gene and cellular therapies. If a patient meets medical necessity as defined by this policy and is approved for treatment, the requesting physician must attest to providing clinical outcome information within the Audaire Health™ provider portal at the requested cadence.

References:

1. Kymriah [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; April 2024.
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4. National Comprehensive Cancer Network. Pediatric acute lymphoblastic leukemia (Version 5.2024). 2024 April 3. Available at: https://www.nccn.org/professionals/physician_gls/pdf/ped_all.pdf. Accessed on April 18, 2024.
5. National Comprehensive Cancer Network. Acute lymphoblastic leukemia (Version 4.2024). 2024 Fab 5. Available at: https://www.nccn.org/professionals/physician_gls/pdf/all.pdf. Accessed on April 18, 2024.
6. National Comprehensive Cancer Network. B-cell lymphomas (Version 1.2024). 2024 Jan 18. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed on April 18, 2024.
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9. Clinicaltrials.gov. A phase II, single arm, multicenter open label trial to determine the efficacy and safety of tisagenlecleucel (CTL019) in adult patients with refractory or relapsed follicular lymphoma (NCT03568461). Available at: https://clinicaltrials.gov/ct2/show/NCT03568461?cond=follicular+lymphoma&intr=%22Kymriah%22+OR+%22Tisagenlecleucel-T%22+OR+%22CTL019%22&draw=2&rank=1. Accessed on March 9, 2022.
10. U.S. Department of Health and Human Services. Common terminology criteria for adverse events (Version 5.0). 2017 Nov 27. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed on July 6, 2022.

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<tr><th>#</th><th>Date</th><th>Change Description</th></tr>
<tr><td>1.7</td><td>Effective Date: 06/06/2024</td><td>Annual review of criteria was performed, no changes were made</td></tr>
<tr><td>1.6</td><td>Effective Date: 06/08/2023</td><td>Updated to require physicians to provide clinical outcomes data using the Audaire Health platform</td></tr>
<tr><td>1.5</td><td>Effective Date: 08/04/2022</td><td>Updated to align criteria across all CAR-T policies and include new indication for use in relapsed/refractory FL</td></tr>
<tr><td>1.4</td><td>Effective Date: 04/14/2022</td><td>Updated to remove CD19 requirement as NCCN guidelines state CAR-T can work without being positivefor CD19 disease and add preliminary criteria for use in relapsed/refractory FL</td></tr>
<tr><td>1.3</td><td>Effective Date: 08/12/2021</td><td>New policy - this policy replaces previously approved criteria that was embedded in Chimeric Antigen Receptor-T Cell Class policy which will be retired</td></tr>
<tr><td>1.2</td><td>Effective Date: 03/08/2018</td><td>UM medical management system update for BCNA and MAPPO
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** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm.*