Subject: Chimeric Antigen Receptor T Cell Therapy (CAR T-cell Therapy): Breyanzi (lisocabtagene maraleucel; liso-cel)		Original Effective Date: 4/5/2021
Policy Number: MCP-400	**Revision Date(s):**	
Review Date:		
MCPC Approval Date: 4/5/2021		

Contents

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members.

The intent of the policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical studies, nationally recognized authoritative references, and current peer-reviewed scientific literature. Molina Healthcare reserves the right to update this policy and revise coverage criteria to include or omit any off-label condition(s) as necessary based on medical literature and clinical studies that may become available. The information outlined in the MCP includes but is not limited to a review of evidence-based information obtained from the following sources Evaluation of New and Existing Technologies (UM 10). This policy is intended to address coverage criteria that are appropriate for most individuals/members with a particular disease, illness, or condition. Each member's unique clinical circumstances may warrant individual consideration, based on review of applicable medical records.

RECOMMENDATION

This policy addresses the use of Breyanzi (lisocabtagene maraleucel; liso-cel), a CD19-directed chimeric antigen receptor (CAR) T-cell therapy, for treatment of relapsed or refractory large B-cell lymphomas (R/R LBCL).

Molina Healthcare reserves the right to update this policy and revise coverage criteria to include or omit any off-label condition(s) as necessary based on medical literature and clinical studies that may become available.

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

Diffuse large B-cell lymphoma (DLBCL) is derived from white blood cells that grow in an uncontrolled, rapid manner and therefore require treatment (LLS, 2021). DLBCL is the most common type of non-Hodgkin lymphoma accounting for approximately 25% of NHL cases and approximately 7 per 100,000 people in the United States is diagnosed with DLBCL annually (UpToDate 2021). Although 5-year survival rates in the first-line setting range from 60% to 70%, up to 50% of patients become refractory to or relapse after treatment (Crump et al. 2017). In eligible patients, high-dose immunotherapy followed by autologous stem-cell transplantation (ASCT) has been the standard of care for relapsed-refractory DLBCL (R/R DLBCL). However, >60% of patients are ineligible for a transplant, and more than half of those undergoing ASCT will subsequently relapse. First-line treatment for DLBCL is based on the combination of the anti-CD20 monoclonal antibody rituximab with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy (WHO, 2016). The addition of rituximab to CHOP significantly improved treatment outcomes, but 30% to 40% of patients are still not cured (ESMO, 2018). **CAR T-cell therapy** offers an additional option for patients with DLBCL. CAR T-cells are a form of immunotherapy in which immune cells are genetically engineered to target an antigen present on tumor cells so that they seek out those cells specifically; these T-cells then initiate an active and sustained immune response against the target cells (Skrabek, P et al. 2019).

Breyanzi (lisocabtagene maraleucel; liso-cel) is indicated for the treatment of adult patients with R/R LBCL after two 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. Breyanzi is not indicated for the treatment of patients with primary central nervous system lymphoma. Breyanzi is a CD19-directed genetically modified autologous cell immunotherapy. The product is administered using a defined ratio of CD4-positive and CD8-positive CAR T cells to reduce variability in CD8-positive and CD4-positive T cell dose. A single dose contains 50 to 110 x 10^6 CAR-positive viable T cells (consisting of 1:1 CAR-positive viable T cells of the CD8 and CD4 components). Breyanzi is the fourth CAR T-cell therapy to receive FDA approval, and the third gene therapy approved for certain types of non-Hodgkin lymphoma, including DLBCL. DLBCL is the most common type of non-Hodgkin lymphoma in adults.

Previous CAR T-cell approvals include Kymriah (tisagenleleucel) for the treatment of R/R LBCL in adults or R/R B-cell acute lymphoblastic leukemia; Yescarta (axicabtagene ciloleucel) for the treatment of R/R LBCL; Tecartus (brexucabtagene autoleucel) for the treatment of adults with R/R mantle cell lymphoma. Kymriah, Yescarta and Breyanzi are indicated for R/R LBCL after two or more lines of systemic therapy.

FDA INDICATIONS

FDA-approved indication does not alone dictate coverage. Molina Clinical Policy may not recommend coverage for all FDA-approved indications. Please review this Policy in its entirety for indications covered by Molina Healthcare.

Large B-cell lymphoma, relapsed or refractory
Treatment of relapsed or refractory large B-cell lymphoma in adults after ≥2 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.

Limitations of use: Not indicated for the treatment of primary central nervous system (CNS) lymphoma

Available as: Breyanzi is supplied in vials as separate frozen suspensions of each CD8 and CD4 component; each component is packed in a carton containing up to 4 vials, depending upon the concentration of the cryopreserved drug product CAR-positive vial T cells.

Approved by the FDA: February 5, 2021

- *Orphan Drug, Regenerative Medicine Advanced Therapy (RMAT) and Breakthrough Therapy designations. Breyanzi is the first regenerative medicine therapy with RMAT designation licensed by the FDA.*

Boxed Warning

- Cytokine release syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving lisocabtagene maraleucel. Do not administer lisocabtagene maraleucel to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab with or without corticosteroids.
- Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving lisocabtagene maraleucel, including concurrently with CRS, after CRS resolution, or in the absence of CRS. Monitor for neurologic events after treatment with lisocabtagene maraleucel. Provide supportive care and/or corticosteroids as needed.
- Risk Evaluation and Mitigation Strategy (REMS): Available only through the BREYANZI REMS

CLASSIFICATION: Antineoplastic Agent, Anti-CD19; Antineoplastic Agent, CAR-T Immunotherapy; CAR-T Cell Immunotherapy; Cellular Immunotherapy, Autologous; Chimeric Antigen Receptor T-Cell Immunotherapy

CENTERS FOR MEDICARE & MEDICAID SERVICES (CMS)

On August 7th, 2019 CMS published a National Coverage Determination (NCD) regarding CAR-T therapy coverage in the Medicare program. According to the NCD, for services performed on or after August 7, 2019, 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. Reference Publication 100-03, National Coverage Determination (NCD) **Manual Section 110.24** for complete coverage criteria. (Rev. 10454, Issued: 11-13-20, Effective: 08-07-19, Implementation: 02-16-21)

NOTE: On 11/2020, a Change Request (CR) was issued to inform of coverage effective for claims with dates of service on or after August 7, 2019 [Link: TN 10454 (Medicare Claims Processing)]

COVERAGE CRITERIA FOR INITIAL AUTHORIZATION

Breyanzi (lisocabtagene maraleucel) may be authorized as one-time treatment course when **ALL** the following criteria are met: [ALL]

1. **Prescriber specialty**

   - ❒ Prescribed by, or in consultation with, an oncologist/hematologist at a certified treatment center

2. **Diagnosis/Indication**

   - ❒ Histologically confirmed diagnosis of CD19-positive large B-cell lymphoma (by testing or analysis confirming CD19 protein on the surface of the B-cell) including ANY of the following types: [ONE]
     - ❍ Diffuse large B-cell lymphoma (DLBCL), not otherwise specified; OR
     - ❍ Transformed DLBCL from indolent histology; OR
     - ❍ High-grade B-cell lymphoma (HGBL); OR
     - ❍ Primary mediastinal large B-cell lymphoma (PMBCL or PMBL); OR
     - ❍ Follicular lymphoma Grade 3B

     NOTE: Breyanzi (lisocabtagene maraleucel) is not indicated for the treatment of patients with primary CNS lymphoma

3. **Age/Gender/Other restrictions [ALL]**

   - ❒ 18 years or older at time of infusion

   - ❒ Women of child-bearing potential
     - ❍ Negative serum pregnancy test within the past 30 days
       AND
     - ❍ Prescriber attestation that member has been counseled on the use of effective contraception during treatment

4. **Step/Conservative Therapy/Other condition Requirements [ALL]**

- ❒ Relapsed or refractory disease, defined as progression after TWO (2) or more lines of systemic therapy (*which may or may not include therapy supported by autologous cell transplant*), including ALL of the following:
  - ❍ Anti-CD20 monoclonal antibody for CD20-positive tumor (e.g. rituximab);

  AND
  - ❍ An anthracycline-containing chemotherapy regimen (e.g. doxorubicin); **or**
  - ❍ For transformed follicular lymphoma: Prior chemotherapy for follicular lymphoma with chemotherapy refractory disease after transformation to DLBCL

- ❒ Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1
  - *Clinical trials excluded patients who are ECOG PS ≥ 2, have CNS involvement, or have serious infections and patients must have adequate organ and marrow function.*
  - *The TRANSCEND study initially allowed individuals with an ECOG score of 2 to enroll, but for unknown reasons, 2 years after study initiation (2017), the protocol was amended to restrict to ECOG of 0 to 1. A total of 4 patients (1% of study population) had ECOG of 2.*

- ❒ Adequate bone marrow, cardiac, pulmonary, and organ function AND deterioration is not expected within four (4) weeks after Breyanzi intravenous infusion, as determined by the treating oncologist/hematologist

  NOTE: Lab results must be submitted within 14 days of authorization confirming that member has adequate organ and bone marrow function

- ❒ If member has a history of allogeneic stem cell transplant: Documentation that member has no signs of active graft versus host disease (GVHD)

- ❒ Clinical notes from member's medical records including: all relevant history and physical exams, disease staging, all prior therapies and cancer treatment history, anticipated treatment course applicable, labs and/or tests supporting the diagnosis (lab results must be dated <u>within 14 days</u> of request)

- ❒ Prescriber attestation that member will <u>not</u> receive ANY of the following:
  - ❍ A G-CSF agent within the first 3 weeks after Breyanzi infusion or until CRS has resolved
    - *Patients may exhibit cytopenias not resolved for several weeks following lymphodepleting chemotherapy and Breyanzi infusion. Grade 3 or higher cytopenias persisted at Day 29 following Breyanzi infusion in 31% (84/268) of patients, and included thrombocytopenia (26%), neutropenia (14%), and anemia (3%).*

  <u>AND</u>
  - ❍ Live virus vaccine for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during Breyanzi treatment and until immune recovery following treatment with Breyanzi

5. Exclusions/*Contraindications

There are no contraindications listed in the manufacturer's labeling

Member must meet the following exclusions criteria:

- ❒ **Absence** of the following conditions: [ALL]
  - ❍ Active inflammatory disorders
  - ❍ Active graft versus host disease (GVHD)
  - ❍ Active hepatitis B virus (HBsAG positive) or active hepatitis C virus (anti-HCV positive) if viral load is detectable; Human immunodeficiency virus (HIV) positive
    NOTE: A history of hepatitis B or hepatitis C is permitted if the viral load is undetectable per quantitative PCR and/or nucleic acid testing
  - ❍ Active, uncontrolled infections (fungal, bacterial, viral, or other uncontrolled infections)
    NOTE: *Uncontrolled or requires IV antimicrobials (antibiotics, antifungals, antiprotozoals, antivirals)
  - ❍ Autoimmune disease requiring systemic immunosuppression
  - ❍ Primary CNS lymphoma
  - ❍ History or presence of CNS disorders (i.e. epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis)
  - ❍ Prior treatment, or being considered for treatment, with CAR-T therapy or other gene therapy; OR repeat administration of Breyanzi
  - ❍ Progressive vascular tumor invasion, thrombosis, or embolism
  - ❍ Vaccination with live virus vaccines within the past 6 weeks (prior to the start of lymphodepleting chemotherapy)
  - ❍ Venous thrombosis or embolism not managed on a stable regimen of anticoagulation

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful but are not sufficient documentation unless ALL specific information required by this MCP are included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and monitoring.

1. Recommended Dosage [ALL]

❒ A treatment course consists of lymphodepleting chemotherapy (consists of fludarabine 30 mg/m^2/day and cyclophosphamide 300 mg/m^2/day concurrently for 3 days) followed by Breyanzi (lisocabtagene maraleucel) 2 to 7 days after completion of lymphodepleting chemotherapy. Confirm availability of autologous lisocabtagene maraleucel prior to initiating lymphodepleting chemotherapy.

- Premedication (acetaminophen and diphenhydramine) is required prior to lisocabtagene maraleucel infusion. Ensure tocilizumab and emergency equipment are available prior to infusion and during recovery period.

❒ Breyanzi (IV infusion only)
- ❍ For autologous use only, administer 2-7 days after completing lymphodepleting chemotherapy
- ❍ **Large B-cell lymphoma, relapsed or refractory: 50 to 110 × 10^6 CAR-positive viable T cells** (consisting of 1:1 CD8 and CD4 components) IV. Actual cell counts and volumes for infusion are on the release for infusion (RFI) certificates.
  - Dose based on the number of CAR-positive viable T-cells per vial. A single dose contains 50-110 x 10^6 CAR-positive viable T-cells.
  - The CD8 and CD4 components are supplied in separate vials; more than 1 vial of each component may be required for a complete dose.

2. Authorization Limit [ALL]

❒ Initial Authorization: ONE (1) single treatment course of Breyanzi per lifetime

❒ Concurrent Authorizations: Authorizations for Breyanzi will also receive approval of **Actemra (tocilizumab).** Max 8 single dose vials per lifetime **[Actemra (tocilizumab) Policy No: C10265-A]**
- Actemra (tocilizumab) is indicated for the treatment of CAR T cell-induced severe or life-threatening CRS in patients ≥ 2 years of age. According to the FDA approved labeling for intravenous tocilizumab, the dose should not exceed 800 mg per infusion every 4 weeks for RA or CRS patients [Actemra (tocilizumab); prescribing information, 2020]

❒ Reauthorization/Continuation of Treatment Authorization: NOT recommended; will not be authorized
- *Repeat administration of CAR-T cell is experimental and investigational since the safety and efficacy beyond one treatment has not been studied and is not indicated in the current FDA approval for Breyanzi. The evidence is insufficient to determine the effects on net health outcomes.*

3. Route of Administration

- ❒ Provider-administered in certified treatment centers enrolled and comply with the REMS requirements
  - Certified healthcare facilities must have on-site, immediate access to tocilizumab.
  - Ensure that a minimum of 2 doses of tocilizumab are available for each patient for infusion within 2 hours after Breyanzi infusion, if needed for treatment of CRS.
  - Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense, or administer Breyanzi are trained on the management of CRS and neurologic toxicities.

REAUTHORIZATION /CONTINUATION OF THERAPY

The safety and efficacy of repeat treatment has not been studied and is currently not supported by any compendia nor indicated in the current FDA approved labeling. Requests for reauthorization or beyond one dose is considered not medically necessary and will not be authorized.

COVERAGE EXCLUSIONS

All other uses of Breyanzi that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy are considered experimental/investigational or not a covered benefit of this policy, including but not limited to the following, due to insufficient evidence in the peer-reviewed medical literature to support safety, efficacy, and net health outcomes. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

- ❒ Primary CNS lymphoma

- ❒ Prior treatment with any form of CAR T-cell therapy, or repeat administration of Breyanzi
  - *Repeat administration of CAR-T cell is experimental and investigational since the safety and efficacy beyond one treatment has not been studied and is not indicated in the current FDA approval for Breyanzi. The evidence is insufficient to determine the effects on net health outcomes.*

- ❒ Pregnancy: Not recommended for women who are pregnant, and pregnancy after Breyanzi infusion should be discussed with the treating physician.
  - *It is not known if Breyanzi has the potential to be transferred to the fetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia and hypogammaglobulinemia.*

- ❒ Pediatric patients: The safety and efficacy of Breyanzi in patients under 18 years of age have not been established.

The FDA based its approval of Breyanzi on data from the TRANSCEND NHL 001 phase 1 trial of 268 patients with R/R LBCL; 192 patients (n=192) were treated with Breyanzi.

- Primary outcome measures included treatment-related adverse events, dose-limiting toxicities and objective response rate. Key secondary outcome measures included complete response rate, duration of response and progression-free survival.
- Of treated patients, 73% achieved a response, including 54% who had minimal or no detectable lymphoma remaining following treatment (complete remission, or CR).
- Of 104 patients treated with Breyanzi who achieved a best overall response of CR, 65% had remission lasting at least 6 months and 62% had remission lasting at least nine months.

TRANSCEND NHL 001

- An open-label, multicenter, pivotal Phase 1 study that assessed the efficacy and safety of Breyanzi in patients (n=269) with R/R LBCL after at least 2 lines of therapy (Abramson et al., 2020).
- Patient population included adult patients [the average age was 63 years (range, 54-70)] with relapsed or refractory large B-cell lymphomas.; a broad range of histological subgroups were included: DLBCL, high-grade B-cell lymphoma with rearrangements of MYC and either BCL2, BCL6, or both (double-hit or triple-hit lymphoma), diffuse large B-cell lymphoma transformed from any indolent lymphoma, primary mediastinal B-cell lymphoma, and follicular lymphoma grade 3B.
- Breyanzi was administered in both inpatient and outpatient.
- Primary endpoints were the incidence of treatment-related adverse events (AEs), the probability of dose-limiting toxicities (DLTs), and the objective response rate (ORR), defined as the proportion of patients who achieved a best overall response of complete response or partial response.
- Key secondary endpoints were the proportion of patients achieving a complete response (CR), the duration of response (DOR), progression-free survival (PFS), and overall survival (OS).
- Primary and secondary end points were met.
- Overall, 256 patients of 344 total patients who underwent leukapheresis were evaluable for efficacy in the study. According to study results:
    - 192 patients were treated with Breyanzi at a dose of 50 to 110 x 10^6 CAR-positive viable T cells and were evaluated for efficacy.
    - Of the treated patients, 73% achieved a response, including 54% with a complete response rate (patient had minimal or no detectable lymphoma remaining following treatment) and 19% who achieved a partial response.
    - Of the 104 patients who achieved complete response, 65% had remission lasting at least 6 months and 62% had remission lasting at least 9 months.
    - The median time to first response was 1 month. The median duration of response was 16.7 months in all responders, and patients who achieved a complete response did not reach a median duration of response. The estimated median duration of response among patients with partial response was 1.4 months.

The labeling carries a boxed warning for CRS, which is a systemic response to the activation and proliferation of CAR T cells, causing high fever and flu-like symptoms and neurologic toxicities. Both CRS and neurological events can be life-threatening. Among 269 patients treated with lisocabtagene maraleucel:

- Most frequent treatment-emergent adverse events were neutropenia (n=169; 63%), anemia (n=129; 48%), fatigue (n=119; 44%), CRS (n=113; 42%), and nausea (n=90; 33%)
- Grade 3 or worse CRS was reported in 2% (6) patients. 1 patient had fatal CRS and 2 had ongoing CRS at time of death.
- Neurological events of any grade occurred in 30% (80) patients. Neurological events occurred during or after CRS in 73% (58) patients. Grade 3 or worse neurological events occurred in 10% (27) patients. 3 patients had fatal neurologic toxicity and 7 had ongoing neurologic toxicity at the time of death.
- The most common toxicities included encephalopathy, tremor, aphasia, delirium, headache, ataxia, and dizziness. Neurologic toxicities resolved in 81 of 95 patients, with a median duration of 12 days.
- Serious AEs occurred in 46% of patients; fatal AEs occurred in 4% of patients

Breyanzi was administered and monitored in the outpatient setting to approximately 10% of patients in this trial. The manufacturer is continuing to evaluate the safety of Breyanzi for outpatient administration and monitoring in the phase II TRANSCEND-OUTREACH 007 and TRANSCEND-PILOT-017006 pilot trials.

Post-Marketing Requirement (PMR) study

A PMR study has been required to further assess long-term safety of Breyanzi and the risk of secondary malignancies occurring after treatment. The multicenter, prospective, observational safety study will include at least 1500 adult patients with R/R large B-cell lymphoma after 2 or more lines of systemic therapy. Patients will be followed for 15 years after treatment with Breyanzi. The primary endpoint will be evaluation for secondary malignancy, which will include the collection and analysis of blood and/or biopsy specimens of certain malignancies for evaluation of insertional mutagenesis.

A digital platform, Cell Therapy 360, is provided by the manufacturer (BMS) to support the patient and physician treatment experience. Patients will be able to track production and receive support and other relevant information. The manufacturer will also provide patients with wearable technology to help patients track their temperature in real time.

Comparative Studies

A head-to-head trial and indirect treatment comparison studies evaluating the safety and efficacy of FDA-approved CAR T-cell therapies are lacking. The differences in patient selection (e.g. prior treatment(s) and transplantation status) and trial design (e.g., use of bridging chemotherapy and different CRS grading scales) make comparisons across the therapies a challenge. According to a final evidence report published by ICER, there is insufficient evidence to conclude the superiority of one CAR T therapy over the other for NHL, particularly because the studies of CAR T therapies are all small, single-arm trials with short follow-up. These limiting factors also make the comparative efficacy analyses versus standard therapy markedly difficult (ICER, March 2018).

- Although there are no comparative studies, a review of the safety data from the pivotal trial shows Breyanzi with a superior safety profile with lower rates of ≥ 3 grade CRS compared with data reported in the pivotal trials of Kymriah and Yescarta:
    - Breyanzi: TRANSCEND NHL-001 trial: 2%
    - Kymriah: JULIET trial: 22%
    - Yescarta: ZUMA-1 trial: 11%

  Breyanzi has notably lower rates of severe CRS and neurotoxicity in the pivotal trial in comparison to Kymriah and Yescarta (though 4 treatment-related deaths occurred) (TRANSCEND-NHL-001).

- Neurologic toxicities occurred in 87% of patients taking Yescarta and 58% of DLBCL patients who were administered Kymriah. Thirty-five percent of patients who received Breyanzi developed neurologic toxicities after administration.

Practice Guidelines and Position Statements

The use of lisocabtagene maraleucel in large B-cell lymphoma has not been addressed in guidelines (March 2021).

National Comprehensive Cancer Network (NCCN) has Clinical Practice Guidelines on B-Cell Lymphomas (Version 1.2021; January 20, 2021) which include Kymriah and Yescarta as options for adult patients with relapsed or refractory large B-cell lymphoma in accordance with FDA approved labeling.

American Society of Clinical Oncology (ASCO) issued a CAR T-Therapy Policy Brief in 2019 supporting coverage of CAR T-cell therapy for all FDA-approved indications.

National Institute for Health and Care Excellence (NICE) is developing guidance on the use of lisocabtagene maraleucel for treating large B-cell lymphoma after at least 2 therapies: Lisocabtagene maraleucel for treating relapsed or refractory aggressive B-cell non-Hodgkin lymphoma [ID1444]
Expected publication date: September 22, 2021

DEFINITIONS

CAR-T cell therapy: Provides engineered molecules called chimeric antigen receptors (CARs) that recognize and destroy antigens present on the surface of lymphoma cells. T cells are removed from patients and genetically modified to produce CARs. The genetically engineered CAR-T cells are grown in the laboratory until they number in the billions and are then infused back into the patient.

Cytokine release syndrome (CRS): An acute systemic inflammatory response syndrome characterized by fever, with or without multiple organ dysfunction that is associated with CAR-T cell therapy or other forms of immunotherapy. Clinical manifestations include fever, which may be accompanied by fatigue, headache, rash, diarrhea, arthralgia, and myalgia. Milder CRS can progress to a more severe syndrome, which may include hypotension, hypoxia, and uncontrolled systemic inflammatory response with circulatory collapse, vascular leakage, peripheral and/or pulmonary edema, renal failure, cardiac dysfunction, and multiorgan system failure.

Eastern Cooperative Oncology Group Performance Status (ECOG PS)

A scale used to determine the individual's level of functioning; standard criteria for measuring how the disease impacts a patient's daily living abilities

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 Deceased

The scale was developed by the Eastern Cooperative Oncology Group (ECOG), now part of the ECOG-ACRIN Cancer Research Group and published in 1982.

Refractory DLBCL: Refers to disease that fails to respond adequately to treatment. Primary refractory DLBCL refers specifically to an inadequate response to initial treatment.

Relapsed DLBCL: Refers to disease that recurs after achievement of a complete response to initial treatment.

APPENDIX

N/A

CODING INFORMATION

The codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is covered or non-covered. coverage is determined by the benefit document. this list of codes may not be all inclusive.

HCPCS	Description
C9399	Unclassified drugs or biologicals (hospital outpatient use)
J3490	Unclassified drugs
J3590	Unclassified biologics
J9999	Not otherwise classified, antineoplastic drugs
CPT Code	**Description**
0537T	Chimeric antigen receptor T-cell (CAR T) therapy; harvesting of blood-derived T lymphocytes for development of genetically modified autologous CAR T-cells, per day
0538T	Chimeric antigen receptor T-cell (CAR T) therapy; preparation of blood-derived T lymphocytes for transportation (e.g., cryopreservation, storage)
0539T	Chimeric antigen receptor T-cell (CAR T) therapy; receipt and preparation of CAR T-cells for administration
0540T	Chimeric antigen receptor T-cell (CAR T) therapy; CAR T cell administration, autologous
96409	Chemotherapy administration; intravenous, push technique, single or initial substance/drug
96413	Chemotherapy administration; intravenous infusion technique; up to 1 hour, single or initial substance/drug
ICD-10	**Description**
C83.30-C83.39	Diffuse Large B-Cell Lymphoma

C82.00-C82.99	Follicular lymphoma
C85.20-C85.29	Mediastinal (thymic) large B-cell lymphoma

REFERENCES

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- NCD for Chimeric Antigen Receptor (CAR) T-cell Therapy (110.24). Available at: CMS NCD
- Decision Memo for Chimeric Antigen Receptor (CAR) T-cell Therapy for Cancers (CAG-00451N) Available at: https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=291

U.S. Food and Drug Administration

- U.S. Food and Drug Administration approves Bristol Myers Squibb's Breyanzi (lisocabtagene maraleucel), a New CAR T Cell Therapy for Adults with Relapsed or Refractory Large B-Cell Lymphoma. [press release]. Bristol Myers Squibb; February 5, 2021.

Clinical Trials

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Policy History	Approval
Policy Developed IRO Peer Review: Policy was reviewed by practicing physician board certified in Internal Medicine, Hematology & Medical Oncology, 3/8/2021	MCPC 4/5/2021

**Annual Review and Policy Revisions: All content, clinical evidence, coverage criteria, practice guidelines, appendices and reference sections were reviewed and revised with the most recent medical literature and*

available evidence. Coverage criteria for Initial and Continuation of Therapy were revised/updated as appropriate.