Subject: Chimeric Antigen Receptor T Cell Therapy (CAR T-cell Therapy): Kymriah (tisagenlecleucel)		Original Effective Date: 4/12/18
Molina Clinical Policy (MCP) Number: MCP-395 (formerly MCP-317a)	**Revision Date(s):** 3/11/19; 4/23/20	
Review Date: 3/11/19; 4/23/20; 2/8/21		
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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.

Recommendation

This policy addresses Kymriah (tisagenlecleucel) for the labeled indications of acute lymphoblastic leukemia (ALL)and diffuse large B-cell lymphoma (DLBCL). The intent of this MCP is to ensure appropriate selection of patients for therapy based on available relevant evidence, product labeling, clinical guidelines, and clinical studies.

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.

Chimeric antigen receptor T-cell therapy (CAR T-cell therapy), a type of immunotherapy which may also be referred to as adoptive T cell therapy, attempts to program individuals' own immune systems to recognize and attack cancer cells. CAR T-cells and genetically engineered TCR T-cells are manufactured by collecting lymphocytes from a patient or donor and modifying them ex vivo through gene transfer techniques. Viral vectors are introduced that express cell receptors that are highly specific for tumor antigens. CAR T and TCR T-cells are then infused back into a patient's body, where they direct a targeted immune response to cancerous tissue. CAR T cells, which are the focus of this report, express a hybrid receptor with an extracellular single-chain antibody fragment, a transmembrane domain, and at least 1 intracellular signaling domain. CAR T-cells are most often used to treat hematological malignancies, and a common target is B-cell cluster of differentiation antigen 19 (CD19). CAR T-cell infusion is typically administered in an outpatient setting, although patients receiving treatment may require an inpatient stay if adverse events are encountered. Patients typically must remain close to the treatment facility or clinic for a period of up to 6-8 weeks for monitoring and rapid identification of treatment-related adverse events that require hospitalization. CAR T therapy is associated with serious complications, including some fatal neurologic events and cytokine release syndrome (CRS), which is a severe systemic response (e.g., high fever, flu-like symptoms, hypotension, mental status changes) to the activation and proliferation of CAR T-cells. CRS is observed in nearly all treated patients and may be life-threatening, but it typically responds to treatment with aggressive supportive care that includes tocilizumab and corticosteroids. Neurologic toxicities may also be severe or life-threatening. Other adverse events include hypersensitivity reactions, serious infections, prolonged cytopenias, prolonged hypogammaglobulinemia, and second malignancies.

Kymriah (tisagenlecleucel) is a CD19-directed genetically modified autologous T cell immunotherapy involving reprogramming an individual's own T cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19-expressing malignant and normal cells. The resulting genetic modified cells express a CD-19 directed chimeric antigen receptor protein that consists of an extracellular portion that has a murine anti-CD19 single-chain antibody fragment as well as an intracellular portion that contains T-cell signaling and co-stimulatory domains. Once injected, the genetically modified T cells selectively targets and binds to CD19 antigen expressed on the surface of B cells and tumors derived from B cells.

Regulatory Status

Kymriah (tisagenlecleucel) is the first CAR T-cell therapy to receive regulatory approval in August 2017.

Acute Lymphoblastic Leukemia (ALL)

Kymriah (tisagenlecleucel) received indication for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse. FDA approval of tisagenlecleucel was based on the ELIANA study, a multicenter clinical trial involving 63 children and young adults with B-cell ALL that had relapsed or resisted treatment. The study was conducted in collaboration with the University of Pennsylvania and Children's Hospital of Philadelphia. The safety and efficacy of tisagenlecleucel were demonstrated in the phase II multicenter ELIANA clinical trial involving 63 pediatric and young adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). The overall remission rate within 3 months of treatment was 83%.

ELIANA is a pivotal open-label, multi-center, single-arm phase II clinical trial. The primary outcome is the overall remission rate, defined as best overall response of complete remission (CR) or CR with incomplete blood count recovery within 3 months. Secondary outcomes included duration of remission, overall survival, and safety. Of the 63 individuals infused with tisagenlecleucel (Kymriah), 52 (83%) achieved complete response and were minimal residual disease (MRD) negative. Duration of remission was defined as the time since onset of complete remission to relapse or death due to underlying cancer, whichever is earlier. A median duration of remission was not reached by any of the 52 individuals. Treatment with tisagenlecleucel has the potential to cause severe side effects. It carries a boxed warning for cytokine-release syndrome, which is a systemic response to the activation and proliferation of CAR T cells causing high fever and flu-like symptoms, and for neurologic events. Both cytokine-release syndrome and neurologic events can be life-threatening. Other severe side effects of tisagenlecleucel include serious infections, hypotension, acute kidney injury, fever, and hypoxia.

Diffuse Large B-cell Lymphoma (relapsed or refractory)

On May 1, 2018, tisagenlecleucel received *expanded approval* by the FDA for the treatment of adults with relapsed or refractory large B-cell lymphoma (including diffuse large B-cell lymphoma [DLBCL] not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma) after two or more lines of systemic therapy. Tisagenlecleucel was granted priority review and breakthrough therapy designations by the FDA. Kymriah is not indicated for the treatment of patients with primary central nervous system lymphoma.

The approval for Kymriah (tisagenlecleucel) for large B-cell lymphoma is supported by data from the pivotal phase II JULIET clinical trial (NCT02445248), the first multi-center global registration study for Kymriah in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). Efficacy and safety of tisagenlecleucel (Kymriah) were established open-label, multicenter, single-arm phase 2 trial of 68 individuals. The study included adults with relapsed or refractory DLBCL who had received 2 or more lines of chemotherapy, including rituximab and anthracycline, or relapsed following autologous hematopoietic stem cell transplantation. Tisagenlecleucel (Kymriah) was administered as a single infusion, following 2-11 days after completion of lymphodepleting chemotherapy. The complete response (CR) rate and partial response (PR) rate was 32% and 18%, respectively; median duration of response was longer in those with CR compared with PR (not reached vs 3.4 months). Median time to first response was 0.9 months (range, 0.7 to 3.3 months).

FDA Indications

Acute lymphoblastic leukemia (relapsed or refractory)

Treatment of B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse in patients up to 25 years of age.

Diffuse large B-cell lymphoma (relapsed or refractory)

Treatment of relapsed or refractory large B-cell lymphoma in adults (after 2 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

Limitation of Use: Kymriah is not indicated for treatment of patients with primary central nervous system lymphoma or for patients with previous treatment with any CAR-T therapy

Available as: Single-dose unit infusion bag: frozen suspension of genetically modified autologous T cells labeled for the specific recipient

Approved by the FDA: August 30, 2017 (ALL); May 1, 2018 (DLBCL)

Boxed Warning

- Cytokine release syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving tisagenlecleucel. Do not administer tisagenlecleucel to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids
- Neurological toxicities, which may be severe or life-threatening, can occur following treatment with tisagenlecleucel, including concurrently with CRS. Monitor for neurological events after treatment with tisagenlecleucel. Provide supportive care as needed

Risk Evaluation and Mitigation Strategy (REMS)
Tisagenlecleucel is available only through the KYMRIAH 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)

National Coverage Determination (NCD) Manual 110.24
(Rev. 10454, Issued: 11-13-20, Effective: 08-07-19, Implementation: 02-16-21)

On August 7th, 2019 CMS published an NCD regarding CAR-T therapy coverage in the Medicare program. According to this NCD, for services performed on or after August 7, 2019, CMS covers autologous (your own blood-forming stem cells are collected) 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.

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)]

Acute Lymphoblastic Leukemia (ALL), Refractory or Relapsed

Kymriah (tisagenlecleucel) may be authorized as a one-time, single administration intravenous infusion when **ALL** the following criteria are met: [ALL]

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

- ❒ Diagnosis of B-cell precursor acute lymphoblastic leukemia (ALL)
  - NOTE: Not indicated for treatment of primary CNS lymphoma

- ❒ Confirmed CD19 protein on the surface of the B-cell by testing or analysis. Documentation required.

- ❒ Required Documentation: [ALL]
  - ❍ Clinical notes from member's medical records including: all relevant history and physical exams, disease staging, all prior therapies and cancer treatment history, labs and/or tests supporting the diagnosis (lab results must be dated within 14 days of request)
    AND
  - ❍ Current weight for review of prescribed dosage

- ❒ 25 years old or younger at time of infusion
  - *Safety and effectiveness in patients 25 years and older have not been established.*

- ❒ Women of child-bearing potential: [ALL]
  - ❍ 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

- ❒ Refractory disease OR 2 or more relapses [*Refractory is defined as failure to achieve a complete response following induction therapy with ≥ 2 cycles of standard chemotherapy regimen (primary refractory) or after 1 cycle of standard chemotherapy for relapsed leukemia (chemorefractory)] **AND** ONE OF THE FOLLOWING: [ONE]
  - ❍ Philadelphia chromosome-negative disease (Ph - ALL); or
  - ❍ Philadelphia chromosome-positive disease (Ph + ALL) AND failure to 2 tyrosine kinase inhibitors (TKIs) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced [e.g. imatinib (gleevac), dasatinib (Sprycel), nilotinib (Tasigna), ponatinib (Iclusig), bosutinib (Bolsulif)]

- ❒ Performance score on Karnofsky or Lansky Scale is greater than or equal to 50%; or Eastern Cooperative Oncology Group (ECOG) performance score is 0-3

- ❒ Adequate bone marrow, cardiac, pulmonary, and organ function AND deterioration is not expected within four (4) weeks after Kymriah 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)

- ❒ Absence of the following conditions:
  - ❍ Active or primary CNS disease
  - ❍ Fungal, bacterial, viral or any active infection(s) that is *uncontrolled, including *but not limited to* the following: TB, Active hepatitis B (HBsAG positive) or hepatitis C (anti-HCV positive), HIV
    - **Uncontrolled or requires IV antimicrobials (antibiotics, antifungals, antiprotozoals, antivirals*)
  - ❍ History or presence of CNS disorder, such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement
    - *NCCN guidelines define CNS involvement (CNS leukemia CNS-3) as the following: a white blood cell (WBC) count of ≥ 5 leukocytes/mcL in the cerebrospinal fluid (CSF) with the presence of lymphoblasts*
  - ❍ Prior treatment with CAR T therapy (i.e. tisagenlecleucel, axicabtagene ciloleucel), or any other gene therapy, or is being considered for treatment with any other gene therapy
  - ❍ Active inflammatory disorders
  - ❍ Active graft versus host disease (GVHD)

- ❒ Member will not receive ANY of the following:
  - ❍ A G-CSF agent within the first 3 weeks after Kymriah infusion or until CRS has resolved; AND
    - *Prolonged neutropenia has been associated with increased risk of infection. Myeloid growth factors, particularly GM-CSF, are not recommended during the first 3 weeks after KYMRIAH infusion or until CRS has resolved.*
  - ❍ Live virus vaccine for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during Kymriah treatment and until immune recovery following treatment with Kymriah

Diffuse Large B-cell Lymphoma (DLBCL)

Kymriah (tisagenlecleucel) may be authorized as a one-time, single administration intravenous infusion when **ALL** the following criteria are met: [ALL]

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

❒ 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**
- ❍ High-grade B-cell lymphoma; **or**
- ❍ DLBCL arising from follicular lymphoma (also referred to as 'follicular lymphoma with histologic transformation to DLBCL)

NOTE: Kymriah (tisagenlecleucel) is not FDA-approved for relapse or refractory primary mediastinal large B-cell lymphoma.

❒ Required Documentation
- ❍ 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); and
- ❍ Current weight for review of prescribed dosage

❒ 18 years or older at time of infusion

❒ Women of child-bearing potential: [ALL]
- ❍ Negative serum pregnancy test within the past 30 days
  <u>AND</u>
- ❍ Prescriber attestation that member has been counseled on the use of effective contraception during treatment

❒ Recent (within the last 30 days) Absolute Lymphocyte Count (ALC) ≥ 300/µL
- *The JULIET trial in patients with DLBCL excluded patients with an ALC <300/µL.*

- ❒ Second or later relapse B-cell lymphoma OR refractory B-cell lymphoma (*with refractory defined as failure to obtain complete response with adequate prior therapy*) with progression after TWO (2) or more lines of systemic therapy (*which may or may not include therapy supported by autologous cell transplant*)
  AND prior therapy including ALL the following: [ALL]
  - ❍ Anti-CD20 monoclonal antibody for CD20-positive tumor (e.g. rituximab);
    AND
  - ❍ An anthracycline-containing chemotherapy regimen and rituximab (e.g. doxorubicin); **or**
  - ❍ For individuals with transformed follicular lymphoma, prior chemotherapy for follicular lymphoma and subsequently have chemorefractory disease after transformation to DLBCL

- ❒ Eastern Cooperative Oncology Group (ECOG) performance status 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.*

- ❒ Adequate bone marrow, cardiac, pulmonary, and organ function AND deterioration is not expected within four (4) weeks after Kymriah 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)

- ❒ Absence of the following conditions:
  - ❍ Active or primary CNS disease
  - ❍ Fungal, bacterial, viral or any active infection(s) that is *uncontrolled, including *but not limited to* the following: TB, Active hepatitis B (HBsAG positive) or hepatitis C (anti-HCV positive), HIV
    **Uncontrolled or requires IV antimicrobials (antibiotics, antifungals, antiprotozoals, antivirals*)
  - ❍ History or presence of CNS disorder, such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement
    - *NCCN guidelines define CNS involvement (CNS leukemia CNS-3) as the following: a white blood cell (WBC) count of ≥ 5 leukocytes/mcL in the cerebrospinal fluid (CSF) with the presence of lymphoblasts*
  - ❍ Vaccination with live virus vaccines within the past 6 weeks (prior to the start of lymphodepleting chemotherapy)
  - ❍ Prior treatment with CART therapy (i.e. tisagenlecleucel, axicabtagene ciloleucel), or any other gene therapy, or is being considered for treatment with any other gene therapy
  - ❍ Active inflammatory disorders
  - ❍ Active graft versus host disease (GVHD)

- ❒ Member will not receive ANY of the following:
  - ❍ A G-CSF agent within the first 3 weeks after Kymriah infusion or until CRS has resolved; AND
    - ◆ *Prolonged neutropenia has been associated with increased risk of infection. Myeloid growth factors, particularly GM-CSF, are not recommended during the first 3 weeks after KYMRIAH infusion or until CRS has resolved.*
  - ❍ Live virus vaccine for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during Kymriah treatment and until immune recovery following treatment with Kymriah

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 [ONE]

Dosage Prescribed must be within the FDA-approved labeling based on member's indication: [ONE]

- ❒ **Diffuse large B-cell lymphoma (relapsed or refractory):** 0.6 to 6 x 10^8 CAR-positive viable T cells IV
  OR
- ❒ **Acute Lymphoblastic Leukemia (relapsed or refractory) [ALL]**
  - ❍ One course of treatment
    - o Lymphodepleting chemotherapy: Fludarabine (30 mg/m^2 intravenous daily for 4 days) and cyclophosphamide (500 mg/m^2 intravenous daily for 2 days starting with the first dose of fludarabine), AND
    - o Kymriah Infusion: Infuse 2 to 14 days after completion of lymphodepleting chemotherapy. Kymriah is provided in a single-dose unit containing chimeric antigen receptor (CAR)-positive viable T cells based on the patient weight reported at the time of leukapheresis

    AND
  - ❍ Pediatric and Young Adult B-cell ALL (up to 25 years of age)
    - o < 25 years of age and weight ≤ 50 kg: administer 0.2 to 5 x 10^6 CAR-positive viable T cells per kg body weight IV, OR
    - o < 25 years of age and weight > 50 kg: administer 0.1 to 2.5 x 10^8 chimeric antigen receptor (CAR)-positive viable T cells IV

2. Authorization Limit [ALL]

- ❒ Initial Authorization: ONE (1) single dose of Kymriah per lifetime
- ❒ Concurrent Authorizations: Authorizations for Kymriah will also receive approval of Actemra (tocilizumab) for a up to 6 months with weight-based dosing as appropriate for the member
- ❒ Continuation of Treatment Authorization: NOT recommended; Refer to Reauthorization
  - ◆ *Repeat administration of tisagenlecleucel is experimental and investigational since the safety and efficacy beyond one dose has not been studied and is not indicated in the current FDA approval for Kymriah. Evidence is insufficient to determine the effects on net health outcomes.*

3. **Route of Administration [ALL]**
   - ❒ Provider-administered medication via IV use only and must be administered in an authorized treatment center: https://www.us.kymriah.com/treatment-center-locator/
   - ❒ The treating facility is certified healthcare facility that is enrolled in, and complies with Kymriah REM requirements, including:
     - ❍ Onsite, immediate access to tocilizumab
     - ❍ Availability of a minimum of two doses of tocilizumab for each patient for administration within 2 hours after Kymriah infusion, if needed for treatment of cytokine release syndrome
     - ❍ Assurance that healthcare providers who prescribe, dispense or administer Kymriah are trained in the management of cytokine release syndrome and neurologic toxicities
     - ❍ Member is within 2 hours of the certified healthcare facility of the Kymriah infusion for at least 4 weeks after treatment
     - ❍ Member will be monitored for signs and symptoms of CRS for at least 4 weeks after treatment with Kymriah and will be counselled to seek immediate medical attention if signs or symptoms of CRS or a neurological event

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 Kymriah (tisagenlecleucel) 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.

- ❑ Follicular lymphoma, relapsed or refractory
  - Tisagenlecleucel is being studied for use in relapsed or refractory follicular lymphoma and is not currently FDA approved for this indication but has been granted the Regenerative Medicine Advanced Therapy (RMAT) designation based on preliminary findings of the ongoing ELARA clinical trial (Novartis FL RMAT Press Release). The RMAT program was developed to allow for expedited development and review of regenerative medicine therapies that are intended for serious conditions.

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

- ❑ Pregnancy: It is not known if Kymriah (tisagenlecleucel) 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. Therefore, Kymriah is not recommended for women who are pregnant, and pregnancy after Kymriah administration should be discussed with the treating physician.

- ❑ Pediatric patients:
  - The safety and efficacy of Kymriah have been established in pediatric patients with *relapsed or refractory large B-cell lymphoma acute lymphoblastic leukemia (ALL).*
  - The safety and efficacy of Kymriah in pediatric patients with *relapsed or refractory DLBCL* has not been established.

- ❑ Geriatric patients: The safety and effectiveness of Kymriah have not been established in geriatric patients with r/r B-cell ALL. Clinical studies of Kymriah did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

SUMMARY OF EVIDENCE

Acute Lymphoblastic Leukemia (ALL)

ALL is an aggressive hematological malignancy in which the bone marrow produces too many immature, non-functional lymphoid cells in the bone marrow, peripheral blood, and other organs. These immature immune cells, known as lymphoblasts, rapidly reproduce and accumulate in the bone marrow, eventually interfering with normal hematopoietic cells. Over time, the lymphoblasts spread into the bloodstream and infiltrate other organs, preventing other cells from performing properly. ALL can originate from B lymphocytes (B cells) or T lymphocytes (T cells). Leukemia is the most common cancer in children, and ALL is the most common cancer in adolescents and young adults under the age of 20, accounting for 18.8% of all cancer cases in this age group (Leukemia and Lymphoma Association). A total of 6150 cases in adult and pediatric patients and 1520 deaths are estimated in the U.S. in 2020 (ACS) with the median age at death of 56 years (NIH). The 5-year survival rate is 68.6% with favorable survival noted in children as prognosis decline with increasing age.

The best available published evidence to date on Kymriah for the treatment of refractory/relapsed ALL in pediatric and young adult patients includes the phase II pivotal ELIANA trial (Maude et al., 2018). Also published is a report on outcomes in patients who were treated in 2 phase I pilot trials (Maude et al., 2014).

ELIANA is the first multicenter global trial to evaluate Kymriah in pediatric and young adult patients with relapsed/refractory B-cell ALL (Maude et al., 2018). A total of 92 patients were enrolled, and 75 underwent treatment with Kymriah (ELIANA; NCT 02435849). Of the 17 patients not treated, 7 died before receiving the infusion, 7 had issues related to the manufacturing of Kymriah, and 3 patients had an adverse event. Of the 75 patients treated, the median age was 11 years (range, 3 to 23 years) and the median number of previous therapies was 3 (range, 1 to 8). A total of 46 patients (61%) had undergone previous allogeneic hematopoietic stem cell transplantation. The median time from trial enrollment to Kymriah infusion was 45 days (range, 30 to 105 days); 65 of the 75 treated patients (87%) received bridging chemotherapy between enrollment and infusion. The primary efficacy endpoint was an overall remission rate > 20% within 3 months of Kymriah infusion. Overall remission

was defined as “best overall response” of either Complete Remission (CR) or incomplete blood count recovery (CRi), and responses had to be maintained for ≥ 4 weeks. The median follow-up time was 13.1 months. The primary efficacy endpoint was achieved by 61 of 75 patients (81%); 45 patients had a CR (60%) and 16 had a CRi (21%). Median duration of response was not yet reached. Relapse-free survival among the 61 patients who responded to Kymriah was 80% at 6 months and 59% at 12 months. The rate of overall survival among the 75 treated patients was 90% at 6 months after infusion and 76% at 12 months after infusion. All 75 treated patients experienced ≥ 1 adverse event (AE), including CRS of any grade (n=58), CRS grade 3 (n=16), and CRS grade 4 (n=19); all CRS events occurred ≤ 8 weeks after Kymriah infusion. A total of 35 patients were admitted to the intensive care unit (ICU) for management of CRS; median ICU stay was 7 days (range, 1 to 34 days). A grade 3 or 4 AE deemed related to Kymriah occurred in 55 patients (73%). Within 8 weeks of treatment with Kymriah, 30 patients (40%) experienced a neurologic AE of any grade, and 10 patients (13%) had a grade 3 neurologic AE. The majority of neurologic AEs occurred during CRS or shortly after CRS resolution. All-cause deaths were reported in 19 patients; 2 deaths occurred within 30 days after infusion.

The safety and efficacy of administering autologous T cells transduced with a CD19-directed chimeric antigen receptor (CTL019) lentiviral vector was studied in a phase II clinical trial of 30 patients (n=30) with relapsed or refractory ALL (Maude et al., 2014). Of the 30 patients, 25 were children and young adults (ages 5 to 22 years) and 5 were older adults (ages 26 to 60 years). All patients received tisagenlecleucel. Complete remission was achieved in 90% (27 patients). CTL019 cells proliferated in vivo and were detectable in the blood, bone marrow, and cerebrospinal fluid of patients who had a response. Sustained remission was achieved with a 6-month event-free survival rate of 67% and an overall survival rate of 78%. At 6 months, the probability that a patient would have persistence of CTL019 was 68% and the probability that a patient would have relapse-free B-cell aplasia was 73%. CRS was noted in all patients with severe CRS developing in 27% of the patients with a higher disease burden before infusion. The anti-interleukin-6 receptor antibody, tocilizumab, effectively treated CRS (Maude, 2014). The authors concluded that CAR T-cell therapy against CD19 was effective in treating relapsed and refractory ALL. CTL019 was associated with a high remission rate. Even amongst patients for whom stem-cell transplantation had failed, durable remissions up to 24 months were observed (CART19 ClinicalTrials.gov numbers, NCT01626495 and NCT01029366).

Teachey et al. (2016) evaluated data from 39 children and 12 adults with refractory/relapsed ALL treated with CTL019. 47 patients (37 pediatric; 10 adults) had B-cell acute lymphoblastic leukemia (B-ALL) in first to fourth relapse, 1 child had relapsed T-cell ALL (T-ALL) with aberrant CD19 expression, and 3 patients (1 pediatric; 2 adults) had primary refractory B-ALL. 31 patients (27 pediatric; 4 adults; 61%) had relapsed after prior allogeneic hematopoietic stem cell transplant (SCT). 4 patients (all pediatric) had previously been treated with blinatumomab, a CD19 BITE antibody. No patient was treated with any other CD19-directed therapy prior to CTL019. Data on response to CTL019 in the first 30 patients (25 children and 5 adults) were recently published, demonstrating a 90% CR rate and a 6-month event-free survival (EFS) rate of 67%.

Fitzgerald et al. (2017) conducted a retrospective cohort study of 39 subjects with relapsed/refractory ALL treated with CAR T-cell therapy on a phase I/IIa clinical trial. The authors noted the following:

- 13 subjects with cardiovascular dysfunction were treated with the interleukin-6 receptor antibody tocilizumab;
- 18 subjects (46%) developed grade 3-4 cytokine release syndrome, with prolonged fever (median, 6.5 d), hyperferritinemia, and organ dysfunction;
- 14 (36%) developed cardiovascular dysfunction treated with vasoactive infusions a median of 5 days after T-cell therapy;
- 6 (15%) developed acute respiratory failure treated with invasive mechanical ventilation a median of 6 days after T cell therapy; 5 met criteria for acute respiratory distress syndrome;
- Encephalopathy, hepatic, and renal dysfunction manifested later than cardiovascular and respiratory dysfunction;
- A median of 15 organ dysfunction days;
- Treatment with tocilizumab in 13 subjects resulted in the rapid subsidence of a fever and clinical improvement. The authors concluded that Grade 3-4 cytokine release syndrome occurred in 46% of patients following T-cell therapy for relapsed/refractory ALL. Growing utilization of this advanced therapy and implications for critical care units in cancer centers are noteworthy factors for consideration by clinicians. (ClinicalTrials.gov number NCT01626495)

Diffuse Large B-Cell Lymphomas (DLBCL)

DLBCL is an aggressive type of non-Hodgkin lymphoma (NHL) that affects B cells, interfering with a patient's immune response and ability to fight infection (Lymphoma Research Foundation, 2020). It is the most common type of NHL in the United States and worldwide with more than 18,000 new cases diagnosed each year (Lymphoma Research Foundation, 2020)

Treatment for Relapsed or Refractory Disease

High-dose chemotherapy followed by stem cell transplantation can be used to treat patients with DLBCL whose disease is refractory or relapsed following initial chemotherapy. Most patients undergoing stem cell transplantation will have an autologous transplant (patient receives his or her own stem cells, collected prior to the procedure). Occasionally, a patient will undergo an allogeneic transplant (patient receives stem cells from a donor).

- **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 (CR) to initial treatment.

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The FDA approval of Kymriah in adult patients with refractory or relapsed DLBCL is based on JULIET, a pivotal phase 2, single-arm, open-label, multicenter, trial of tisagenlecleucel in adults with refractory or relapsed DLBCL. Kymriah showed an overall response rate (ORR) of 50%, with 32% of patients achieving a complete response (CR) and 18% achieving a partial response (PR) in 68 patients evaluated for efficacy. The median duration of response was not reached among these patients, indicating sustainability of response In all patients infused with Kymriah (n=106), severe or life-threatening (grade 3/4) CRS, defined by the Penn Grading Scale a rigorous scale for grading this reaction, occurred in 23% of patients. CRS is a known complication of CAR-T therapy that may occur when the engineered cells become activated in the patient's body. CRS was managed globally using prior site education on implementation of the CRS treatment algorithm. 18% of all infused patients experienced grade 3/4 neurologic events, which were managed with supportive care. Encephalopathy, a distinctive neurotoxicity associated with CAR-T therapies, was severe or life-threatening in 11% of patients. There were no deaths attributed to neurological events, and no fatal cases of cerebral edema have occurred. Grade 3/4 cytopenias lasting more than 28 days included thrombocytopenia (40%) and neutropenia (25%), and grade 3/4 infections occurred in 25%. The most common (>20%) adverse events in the JULIET study are CRS, infections, pyrexia, diarrhea, nausea, fatigue, hypotension, edema and headache.

The manufacturer has agreed to a post-marketing requirement observational registry study to collect safety information for patients treated with the marketed product. To further evaluate the long-term safety and the risk of secondary malignancies occurring after treatment, the FDA is requiring the manufacturer to conduct a post-marketing observational study involving patients treated with Kymriah (tisagenlecleucel). This study will include at least 1500 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. The enrolled patients will be followed for 15 years after the product administration.

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)

The following recommendations for the use of tisagenlecleucel (Kymriah) is discussed in the National Comprehensive Cancer Network Drugs and Biologics Compendium (NCCN, 2020):

Acute Lymphoblastic Leukemia (ALL) Guidelines

- The guideline mentioned the FDA indication for tisagenlecleucel is patients < 26 years of age and CD19+ B-cell ALL that is refractory or with 2 or more relapses.
- The clinical decision chart provides some level 2B recommendations (based on lower-level evidence and interventions deemed appropriate by the NCCN) for the specific uses of tisagenlecleucel.
- Patients are strongly recommended to undergo tisagenlecleucel or other CAR T-cell therapy in the context of a clinical trial setting.
- Recommendations for lymphodepletion regimens and adverse event management are discussed

NCCN guidelines for **ALL** (version 1.2020) address Kymriah:

- For Philadelphia chromosome-positive B-cell ALL: Kymriah is cited as a treatment option for individuals < 26 years of age and with refractory disease or ≥ two relapses and failure of two tyrosine kinase inhibitors (TKIs) [category 2A]
- For Philadelphia chromosome-negative B-cell ALL: Kymriah is listed as a therapy option for individuals < 26 years of age and with refractory disease or ≥ two relapses (category 2A)

NCCN guidelines for **Pediatric ALL** (version 2.2020 – November 25, 2019) recommends Kymriah for:

- For the treatment of individuals with refractory or ≥ 2 relapses, TKI intolerant or refractory disease, or relapse post-hematopoietic stem cell transplantation (category 2A)
- For individuals who are minimal residual disease positive (MRD+) after consolidation therapy, and in Philadelphia chromosome-positive disease with less than complete response, or high-risk genetics (Category 2B)

B-Cell Lymphomas

- The NCCN guidelines for B-cell lymphomas (version 1.2020 – January 22, 2020) recommend Kymriah for the treatment of the following relapsed or refractory disease after at least two course of systemic therapy: DLBCL following transformation from follicular lymphoma or nodal marginal zone lymphoma, DLBCL, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, AIDS-related B-cell lymphoma, human herpes virus 8 (HHV8)-positive DLBCL, and post-transplant lymphoproliferative disorders (category 2A)

- Diffuse Large B-Cell Lymphoma (DLBCL) used or diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma as:
    - Additional therapy for patients with intention to proceed to transplant who have partial response following second-line therapy for relapsed or refractory disease [2A]
    - Treatment (if anti-CD19 CAR T-cell therapy was not previously given) of disease in second relapse or greater in patients with partial response, no response, or progressive disease following therapy for relapsed or refractory disease [2A]

- Histologic Transformation of Nodal Marginal Zone Lymphoma to Diffuse Large B-Cell Lymphoma as preferred therapy (if anti-CD19 CAR T-cell therapy was not previously given) for patients who have received multiple lines of prior therapies including ≥2 chemoimmunotherapy regimens for indolent or transformed disease (patients should have received at least one anthracycline or anthracenedione-based regimen, unless contraindicated) [2A].

- High-Grade B-Cell Lymphomas - used for high-grade B-cell lymphomas with translocations of MYC and BCL2 and/or BCL6 (double/triple hit lymphoma) or high-grade B-cell lymphomas, not otherwise specified as:
    - Additional therapy for patients with intention to proceed to transplant who have partial response following second-line therapy for relapsed or refractory disease [2A]

- Treatment (if anti-CD19 CAR T-cell therapy was not previously given) of disease in second relapse or greater in patients with partial response, no response, or progressive disease following therapy for relapsed or refractory disease [2A].

- Follicular Lymphoma (grade 1-2) for treatment of histologic transformation to diffuse large B-cell lymphoma (DLBCL) in patients who have received:
  - Minimal or no chemotherapy prior to histologic transformation to DLBCL and have partial response (preferred in patients with partial response), no response, or progressive disease after treatment with ≥2 chemoimmunotherapy regimens which included at least one anthracycline or anthracenedione-based regimen, unless contraindicated [2A]
  - Multiple lines of prior therapies (not including axicabtagene ciloleucel or tisagenlecleucel) for indolent or transformed disease (only after treatment with ≥2 chemoimmunotherapy regimens which included at least one anthracycline or anthracenedione-based regimen, unless contraindicated) [2A].

American Society for Blood and Marrow Transplantation (ASBMT)

A global CAR-T Task Force developed an expert opinion report addressing the primary challenges in the treatment and management of patients with relapsed or refractory B-ALL treatment with CAR-T cell therapy. The Task Force included representatives from the ASBMT, European Society for Blood and Marrow Transplantation (EBMT), the International Society of Cell and Gene Therapy, and the Foundation for the Accreditation of Cellular Therapy. The report discussed the 'robust clinical infrastructure to handle the complex scheduling logistics to facilitate communication and manage potential severe toxicity' of CAR T-cell therapy. The authors concluded that 'Data regarding CAR-T late effects are still limited. Detection of these effects requires ongoing long-term follow-up and enhanced clinical awareness by clinicians caring for patients after CAR-T therapy worldwide. A 15-year follow-up is requested as part of the marketing authorization of tisagenlecleucel and axicabtagene ciloleucel, both by the FDA and European Medicines Agency.' (Kansagra et al., 2019)

CAR T-cell therapy-associated TOXicity (CARTOX) Working Group

CARTOX published the guideline called Chimeric antigen receptor T‑cell therapy assessment and management of toxicities (Neelapu et al., 2017). The guidelines summarize the two major toxicity's associated with CAR T therapy: Cytokine-release syndrome (CRS), the most commonly observed toxicity, can range in severity from low-grade constitutional symptoms to a high-grade syndrome associated with life-threatening multi-organ dysfunction; rarely, severe CRS can evolve into fulminant haemophagocytic lymphohistiocytosis (HLH). Neurotoxicity, termed CAR T-cell-related encephalopathy syndrome (CRES), is the second most-common adverse event, and can occur concurrently with or after CRS. The guidelines recommend that intensive monitoring and prompt management of toxicities is essential to minimize the morbidity and mortality associated with this potentially curative therapeutic approach that include a multidisciplinary approach to provide recommendations for monitoring, grading, and managing the acute toxicities that can occur in patients treated with CAR T-cell therapy.

The Foundation for the Accreditation of Cellular Therapy (FACT)

FACT is a U.S. based program that oversees the accreditation of centers that perform stem cell transplants and other types of cell-based therapies such as quality aspects of cellular therapy. The group published guidelines in 2018 'FACT Standards for Immune Effector Cells' which apply to cells used to modulate an immune response for therapeutic intent, including CAR T cells. These standards are designed to provide the requirements and minimum guidelines for programs, facilities, and individuals performing cell transplantation and therapy or providing support services for such procedures.

The Institute for Clinical and Economic Review (ICER)

ICER published the final evidence report (March 2018), "Chimeric Antigen Receptor T Cell Therapy for B-Cell Carcinoma: Effectiveness and Value." Compared with the outcomes of patients receiving other similar FDA-indicated therapies, ICER reviewed the outcome of tisagenlecleucel in B-ALL and NHL, and the outcome of axiabtagene ciloleucel in NHL. It is noted that 'evidence is insufficient to conclude the superiority of one CAR T therapy to the other for NHL. In general, the findings suggest that the CAR T therapies provide a net health benefit compared to standard chemoimmunotherapy regimens and found both therapies to be cost-effective in the long-term for the specified indications.' However, studies of CAR T therapies are single-arm trials with small sample sizes and short duration of follow-up which makes the comparative efficacy analyses versus standard therapy uncertain and controversial.

DEFINITIONS

Anti-CD20 monoclonal antibodies (mAbs): Used to achieve B cell depletion and were initially developed to treat B cell proliferative disorders, including non-Hodgkin's lymphoma and chronic lymphocytic leukemia.

Cytokine release syndrome (CRS):

- CRS is a systemic inflammatory response syndrome triggered in particular by the release of large amounts of interleukin-6. The release of cytokines induces fever, vascular leakage, and potentially direct myocardial injury. CRS is the most common toxicity associated with CAR T-cell therapy usually develops in the first or second week after CAR T infusion.
- The severity of CRS symptoms can vary significantly, ranging from low grade with mild symptoms to high grade with early-onset high fevers, hyperpyrexia, high incidence of infections, and neurotoxicity. Moreover, severe CRS can be accompanied by excessive macrophage activation, coagulation dysfunction, tumor lysis syndrome, and involve any organ system in the body and lead to life-threatening multiorgan dysfunction including the cardiovascular, nervous, respiratory, gastrointestinal, hepatic, renal, and hematological systems
- In terms of management, mild to moderate CRS is usually self-limited and can be controlled with close observation, hydration, and supportive care. In contrast, severe CRS requires intensive medical management with tocilizumab alone or in combination with steroids.

ECOG (Eastern Cooperative Oncology Group)

Performance Status: A scale used to determine the individual's level of functioning; may also be referred to as the WHO (World Health Organization) or Zubrod score:

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

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 (CR) to initial treatment.

APPENDIX

N/A

CODING INFORMATION: THE CODES LISTED IN THIS CLINICAL POLICY ARE FOR INFORMATIONAL PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE AND INCLUSION OR EXCLUSION OF ANY CODES DOES NOT GUARANTEE COVERAGE. PROVIDERS SHOULD REFERENCE THE MOST UP-TO-DATE SOURCES OF PROFESSIONAL CODING GUIDANCE PRIOR TO THE SUBMISSION OF CLAIMS FOR REIMBURSEMENT OF COVERED SERVICES.

HCPCS	Description
Q2042	Tisagenlecleucel, up to 600 million CAR-positive viable T cells, including leukapheresis and dose preparation procedures, per therapeutic dose
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
ICD-10	**Description**
C82.00-C82.99	Follicular lymphoma
C83.30-C83.39	Diffuse large B-cell lymphoma
C85.20-C85.29	Mediastinal (thymic) large B-cell lymphoma
C91.00-C91.02	Acute lymphoblastic leukemia (ALL)

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Policy History	Approval
Previous policy (MCP-317) included both Kymriah and Yescarta; created individual policy for Kymriah (MCP-317a) and Yescarta (MCP-317b). AMR Peer Review: Policy was reviewed by practicing physician board certified in Internal Medicine, Oncology, Hematology, 11/21/2017	
Policy Developed	4/12/2018
Policy Revision AMR Peer Review: Policy was reviewed by practicing physician board certified in Internal Medicine, Oncology, Hematology, 1/28/2019 • Added indication of Diffuse Large B-cell Lymphoma (DLBCL) indication to all applicable sections in policy. • Policy was reviewed in its entirety with all clinical evidence, coverage criteria, practice guidelines, appendices and reference sections of the policy 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.	3/11/2019
Policy Revision* AMR Peer Review: Policy was reviewed by practicing physician board certified in Oncology, Hematology, 4/3/2020 Notable revisions include: • Added criterion for women of child-bearing potential requiring a negative pregnancy test • Added '*Lab results must be submitted within 14 days of the authorization*' to criterion confirming that member has adequate organ and bone marrow function • Added criteria to DLBCL indication to include 'Absolute lymphocyte count (ALC) ≥ 300/µL' • Updated criteria in the 'Recommendation' section '*Member does NOT meet or have any of the following conditions*' to include '*Active central nervous system (CNS) lymphoma by imaging*' and '*Vaccination with live virus vaccines within the past 6 weeks (prior to the start of lymphodepleting chemotherapy)*' • Updated NCCN Clinical Practice Guidelines	4/1/2020
Annual Review* The medical necessity criteria were not revised with this annual review Content changes include: • Added 'follicular lymphoma, relapsed or refractory' as a coverage exclusion • Updated NCCN guidelines: B-cell ALL and for B-cell lymphoma • Added an expert opinion report from a global CAR-T Task Force addressing the primary challenges in the treatment and management of patients with relapsed or refractory B-ALL treatment with CAR-T cell therapy (European Society for Blood and Marrow Transplantation and the American Society for Blood and Marrow Transplantation) • Insertion of a CMS Section outlining the NCD for implementation on 02-16-21 • Policy number updated to MCP-395 (from 317a) for clarity [Historical information: First policy developed was MCP-317 which included both Kymriah and Yescarta. Committee voted to split into individual policies for Kymriah (MCP-317a) and Yescarta (MCP-317b)]	MCPC 2/8/21

**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.*