| Subject: Chimeric Antigen Receptor T cell Therapy (CAR-T Cell Therapy): Kymriah (Tisagenlecleucel) | | Original Effective Date: 4/12/2018 |
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## DISCLAIMER

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## DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

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.

### Kymriah (tisagenlecleucel)

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 became the first chimeric antigen receptor T (CAR-T) cell therapy to receive regulatory approval in August 2017, when it was approved by the US FDA 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, based on previous results from the ELIANA study, which 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.

- 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.

  Efficacy and safety of tisagenlecleucel (Kymriah) were established in a retrospective subgroup analysis of an open-label, single-arm trial (JULIET) 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).

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

**Kymriah (tisagenlecleucel) is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS).** Mandatory program required by the U.S. FDA to administer Kymriah (tisagenlecleucel) to manage the known and potential serious risks associated with the therapy and to ensure that the benefits of treatment outweigh its risks, including cytokine release syndrome (CRS) and neurological toxicities. The required components of the KYMRIAH REMS include:

- According to the black box warning in the FDA Product Information Label, tisagenlecleucel should be administered at a designated treatment center that has received site certification.
- Healthcare facilities that dispense and administer tisagenlecleucel must have on-site, immediate access to a minimum of two doses of tocilizumab for administration within 2 hours after infusion, if needed for treatment of CRS.
- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer tisagenlecleucel are trained in the management of CRS and neurological toxicities.
- Patients treated with CAR-T cell therapy 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.

**RECOMMENDATION**

**B-cell precursor Acute Lymphoblastic Leukemia (ALL), Refractory or relapsed**

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

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

- ❒ Required Documentation:
  - ❍ Clinical notes from the 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 within 14 days of request); and
  - ❍ Current weight for review of prescribed dosage

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

- ❒ Diagnosis B-cell precursor acute lymphoblastic leukemia (ALL)

- ❒ Confirmed CD19-positive B-cell precursor acute lymphoblastic leukemia (by testing or analysis confirming CD19 protein on the surface of the B-cell). Documentation required.

- ❒ Refractory disease or 2 or more relapses AND one of the following subtypes:
  - ❍ Philadelphia chromosome-negative disease (Ph - ALL); or
  - ❍ Philadelphia chromosome-positive disease (Ph + ALL) and failure to 2 tyrosine kinase inhibitors (TKIs) (e.g. imatinib (gleevac), dasatinib (sprycel), nilotinib (tasigna), ponatinib (iclusig), bosutinib (bolsulif); AND

- ❒ 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; and

- ❒ Member has 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

- ❒ Absence of active infection (including TB, HBV, HCV, and HIV) or inflammatory disorders; and

- ❒ Member has not received prior CAR-T therapy (i.e. tisagenlecleucel, axicabtagene ciloleucel), or any other gene therapy, or is being considered for treatment with any other gene therapy; and

- ❒ If member has a history of allogeneic stem cell transplant, has no signs of active graft versus host disease

- ❒ Dosage prescribed is within the FDA-approved labeling based on indication of Acute Lymphoblastic Leukemia (ALL):
  - ❍ One treatment course consists of lymphodepleting chemotherapy [Fludarabine (30 mg/$m^2$ intravenous daily for 4 days) and cyclophosphamide (500 mg/m2 intravenous daily for 2 days starting with the first dose of fludarabine within two weeks preceding Kymriah infusion], followed by a single infusion of Kymriah with the recommended dose:
    1) Acute lymphoblastic leukemia (relapsed or refractory)
       - < 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
       - < 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) Diffuse large B-cell lymphoma (relapsed or refractory): 0.6 to 6 x $10^8$ CAR-positive viable T cells IV

- Initial/Continuation of Treatment
  - Initial Authorization: ONE (1) single-dose of Kymriah per lifetime
  - Authorizations for Kymriah will also receive approval of Actemra (tocilizumab) for a period of 6 months. If severe or life-threatening cytokine-release syndrome is suspected (CRS), administer tocilizumab as either 12mg/kg IV over 1 hour for patients <30kg or 8mg/kg IV over 1 hour for patients ≥30kg
  - Continuation of Treatment Authorization: NOT recommended

- The treating facility is certified healthcare facility that is enrolled 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

## Diffuse Large B-cell Lymphoma (DLBCL)

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

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

- ❒ 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 within 14 days of request); and
  - ❍ Current weight for review of prescribed dosage

- ❒ 18 years or older at time of infusion; and

- ❒ 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,
  - ❍ Diffuse large B-cell lymphoma (DLBCL), not otherwise specified; **or**
  - ❍ High-grade B-cell lymphoma; **or**
  - ❍ DLBCL arising from follicular lymphoma; **and**

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

- ❒ 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 of the following:
  - ❍ 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**; and**

- ❒ Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; **and**
  - ◆ *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.*

- ❒ Member has 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

- ❒ Absence of active infection (including TB, HBV, HCV, and HIV) or inflammatory disorders; and

- ❒ Member has not received prior CAR-T therapy (i.e. tisagenlecleucel, axicabtagene ciloleucel), or any other gene therapy, or is being considered for treatment with any other gene therapy; and

- ❒ Member has adequate organ and bone marrow function as determined by the Prescriber, the treating oncologist/hematologist

- ❒ Dosage prescribed is within the FDA-approved labeling based on indication of **diffuse large B-cell lymphoma (relapsed or refractory):** 0.6 to 6 x $10^8$ CAR-positive viable T cells IV; and

- ❒ Initial/Continuation of Treatment
  - ❍ Initial Authorization: ONE (1) single-dose of Kymriah per lifetime
  - ❍ Authorizations for Kymriah will also receive approval of Actemra (tocilizumab) for 4 doses over a duration of 3 months
  - ❍ Continuation of Treatment Authorization: NOT recommended

- ❒ The treating facility is certified and complies with the KYMRIAH REMS System program, 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

## CONTINUATION OF THERAPY

CAR-T cell therapy is indicated to be dosed and infused one time only. Repeat treatment in individuals who have received CAR-T treatment previously is not supported by compendia and not considered not medically necessary.

## 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.

- ❑ Members who have had prior treatment with any form of CAR-T cell therapy
  - ◆ *Repeat administration of tisagenlecleucel 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: There are no available data with Kymriah use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with Kymriah to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known if Kymriah have the potential to be transferred to the fetus. Therefore, Kymriah is not recommended for women who are pregnant.

- ❑ 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 <u>not</u> 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.

**Kymriah (Tisagenlecleucel) for Acute Lymphoblastic Leukemia (ALL)**

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).

Maude et al., 2018

ELIANA is the first multicenter global trial to evaluate Kymriah in pediatric and young adult patients with relapsed/refractory B-cell ALL. 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.

Maude et al., 2014

In 2014, Maude and colleagues published the results of a phase II clinical trial in children and adults diagnosed with relapsed/refractory ALL (n=30). A total of 25 children and young adults (5-22 years of age) and 5 older adults (26-60 years of age) received tisagenlecleucel. Complete Remission (CR) was achieved in 27 study participants (90%), including 2 with blinatumomab-refractory disease and 15 who had previously undergone stem-cell transplantation. There was a 6-month event-free survival rate of 67% (95% CI, 51-88%) and an OS rate of 78% (95% CI, 65-95). All study participants developed CRS. Severe CRS developed in 27% of participants and was associated with a higher disease burden prior to infusion. CRS was effectively treated with the anti-interleukin-6 receptor antibody, tocilizumab (Maude, 2014).

The safety and efficacy of administering autologous T cells transduced with a CD19-directed chimeric antigen receptor (CTL019) lentiviral vector was assessed in 30 children and adults with relapsed or refractory acute lymphoblastic leukemia (ALL). Doses of 0.76×10(6) to 20.6×10(6) CTL019 cells per kilogram of body weight were administered and patients were monitored for a response, toxic effects, and the expansion and persistence of circulating CTL019 T cells. Complete remission was achieved in 27 patients (90%), including 2 patients with blinatumomab-refractory disease and 15 who had undergone stem-cell transplantation. 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% (95% confidence interval [CI], 51 to 88) and an overall survival rate of 78% (95% CI, 65 to 95). At 6 months, the probability that a patient would have persistence of CTL019 was 68% (95% CI, 50 to 92) and the probability that a patient would have relapse-free B-cell aplasia was 73% (95% CI, 57 to 94). All the patients had the cytokine-release syndrome. Severe cytokine-release syndrome, which developed in 27% of the patients, was associated with a higher disease burden before infusion and was effectively treated with the anti-interleukin-6 receptor antibody tocilizumab. The authors concluded that chimeric antigen receptor-modified T-cell therapy against CD19 was effective in treating relapsed and refractory ALL. CTL019 was associated with a high remission rate, even among patients for whom stem-cell transplantation

had failed, and durable remissions up to 24 months were observed. (Funded by Novartis and others; 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. Forty-seven patients (37 pediatric; 10 adults) had B-cell acute lymphoblastic leukemia (B-ALL) in first to fourth relapse, 1 child had relapsed T-cell acute lymphoblastic leukemia (T-ALL) with aberrant CD19 expression, and 3 patients (1 pediatric; 2 adults) had primary refractory B-ALL. Thirty-one patients (27 pediatric; 4 adults; 61%) had relapsed after prior allogeneic hematopoietic stem cell transplant (SCT). Four 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: In a retrospective cohort study thirty-nine subjects with relapsed/refractory acute lymphoblastic leukemia were treated with chimeric antigen receptor-modified T cell therapy on a phase I/IIa clinical trial (ClinicalTrials.gov number NCT01626495). All subjects received chimeric antigen receptor-modified T cell therapy. Thirteen subjects with cardiovascular dysfunction were treated with the interleukin-6 receptor antibody tocilizumab. Eighteen subjects (46%) developed grade 3-4 cytokine release syndrome, with prolonged fever (median, 6.5 d), hyperferritinemia (median peak ferritin, 60,214 ng/mL), and organ dysfunction. Fourteen (36%) developed cardiovascular dysfunction treated with vasoactive infusions a median of 5 days after T cell therapy. Six (15%) developed acute respiratory failure treated with invasive mechanical ventilation a median of 6 days after T cell therapy; five met criteria for acute respiratory distress syndrome. Encephalopathy, hepatic, and renal dysfunction manifested later than cardiovascular and respiratory dysfunction. Subjects had a median of 15 organ dysfunction days (interquartile range, 8-20). Treatment with tocilizumab in 13 subjects resulted in rapid defervescence (median, 4 hr) 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 acute lymphoblastic leukemia. Clinicians should be aware of expanding use of this breakthrough therapy and implications for critical care units in cancer centers.

**Kymriah (Tisagenlecleucel) for Large B-Cell Lymphomas**

Expanded FDA approval of Kymriah (tisagenlecleucel) for the treatment of large B-cell lymphoma was based on the Phase II JULIET clinical trial, a single-arm, open-label, multi-center study in adults with relapsed or refractory DLBCL (NCT 02445248). The JULIET clinical trial is the first multi-center global registration study for Kymriah in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). JULIET was conducted in collaboration with Penn, and is the largest study examining a CAR-T therapy in DLBCL, enrolling patients from 27 sites in 10 countries across the United States, Canada, Australia, Japan and Europe, including: Austria, France, Germany, Italy, Norway and the Netherlands. In the JULIET trial, patients were infused in the inpatient and outpatient setting.

Eligible patients were ≥ 18 years of age with relapsed or refractory DLBCL, who receive ≥ 2 lines of chemotherapy, including rituximab and anthracycline, or relapsed following autologous hematopoietic stem cell transplantation (HSCT). The study excluded patients with active central nervous system malignancy, prior allogeneic HSCT, and ECOG performance status ≥ 2, a creatinine clearance < 60, alanine aminotransferase > 5 times normal, cardiac ejection fraction < 45%, or absolute lymphocyte concentration less than 300/uL. Of the 160 patients enrolled, 106 patients received tisagenlecleucel, including 92 patients who received product manufactured in the U.S. and were followed for at least 3 months or discontinued earlier. Eleven out of 160 patients enrolled did not receive tisagenlecleucel due to manufacturing failure. Thirty-eight other patients did not receive tisagenlecleucel, primarily due to death (n=16), and adverse events (n=3). Of the 92 patients receiving Kymriah, 90% received physician's choice of bridging chemotherapy in the interval between start of screening and Kymriah infusion, among whom the median number of bridging chemotherapy regimens was 1 (range: 1 to 5) with 83% of patients receiving ≤ 2 regimens. A retrospectively identified sub-group of 68 patients was evaluable for the major efficacy outcome measures. Patients included in this sub-group had either no bridging chemotherapy, or had imaging that showed measurable disease after completion of bridging chemotherapy, prior to Kymriah infusion. Of the 24 patients not included, 8 had no evidence of disease at baseline prior to Kymriah infusion, 15 did not have baseline imaging following bridging chemotherapy, and I was excluded because of initial misclassification of a neuroendocrine tumor as DLBCL.

Among the efficacy evaluable population of 68 patients, the baseline characteristics were: median age 56 years (range 22 to 74 years); 71% male; 90% White, 4% Asian, and 3% Black or African American; 78% had primary DLBCL not otherwise specified (NOS) and 22% had DLBCL following transformation from follicular lymphoma, of whom 17% were identified as high grade; and 44% had undergone prior autologous HSCT. The median number of prior therapies was 3 (range 1 to 6), 56% had refractory disease and 44% relapsed after their last therapy. Ninety percent of patients received lymphodepleting chemotherapy (LD) (66% of patients received fludarabine and 24% received bendamustine) and 10% did not receive any LD chemotherapy. The median time from leukapheresis and cryopreservation to Kymriah infusion was 113 days (range 47 to 196 days). The median dose was $3.5 \times 10^8$ CAR-positive viable T cells (range 1.0 to $5.2 \times 10^8$ cells). Seventy-three percent of patients received Kymriah in the inpatient setting. Efficacy was established on the basis of complete response (CR) rate and duration of response (DOR), as determined by an independent review committee. The median time to response to Kymriah (CR and PR (partial 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 1months, 12 more by month 3, and the last by month 6 after Kymriah infusion. In this Novartis-sponsored study, Kymriah showed an overall response rate (ORR) of 50% (95% confidence interval (CI), 38% to 62%), with 32% of patients achieving a complete response (CR) and 18% achieving a partial response (PR). In all patients infused with Kymriah severe or life threatening (grade 3/4) CRS (cytokine release syndrome), defined by the Penn Grading Scale a rigorous scale for grading this reaction, occurred in 23% of patients. CRS is 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. Eighteen percent of all infused patients experienced grade 3/4 neurologic events, which were managed with supportive care. Encephalopathy, a distinctive neurotoxicity associated CAR-T therapies, was seen as 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 (AEs) in the JULIET study are CRS (cytokine release syndrome), infections, pyrexia, diarrhea, nausea, fatigue, hypotension, edema and headache.

Summary: The approval for Kymriah (tisagenlecleucel) is supported by data from the JULIET phase II clinical trial (NCT02445248), the first multi-center global registration study for Kymriah (tisagenlecleucel) in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). In this Novartis-sponsored study, Kymriah (tisagenlecleucel) showed an overall response rate (ORR) of 50% (95% confidence interval (CI), 38% to 62%), 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. This FDA approval brings an additional treatment option for these patients with few other options that have not responded to previous treatments, to include unsuccessful autologous stem cell transplant. The most common (> 20%) adverse events (AEs) in the JULIET study are CRS (cytokine release syndrome), infections, pyrexia, diarrhea, nausea, fatigue, hypertension, edema, and headache. Due to the risk of CRS and neurologic toxicities, Kymriah (tisagenlecleucel) was approved with a Risk Evaluation and Mitigation Strategy (REMS), which includes elements of safe use.

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 diffuse large B-cell lymphoma (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.

**PROFESSIONAL SOCIETY GUIDELINES**

**NCCN: Acute Lymphoblastic Leukemia Version 1.2018**

Relapsed/Refractory Disease

- Ph+ ALL (Adolescent/Young Adult & Adult) → ABL1 kinase domain mutation testing → Treatment
  - Clinical trial; or
  - TKI ± chemotherapy; or
  - TKI ± corticosteroids; or
  - Blinatumomab (TKI intolerant/refractory); or
  - Inotuzomab ozogamicin (TKI intolerant/refractory); or
  - Tisagenlecleucel (patients < 26 years and with refractory disease or ≥ 2 relapses and failure of 2 TKIs)
- Ph- ALL (Adolescent/Young Adult & Adult) → Treatment
  - Clinical trial; or
  - Blinatumomab (category 1); or
  - Inotuzumab ozogamicin (category 1); or
  - Tisagenlecleucel (patients < 26 years and with refractory disease or ≥ 2 relapses); or
  - Chemotherapy

Patients with Relapsed/Refractory Ph Positive ALL

Tisagenlecleucel is also an option for patients up to age 25 years (age < 26 years) and with refractory disease or ≥ 2 relapses and failure of 2 TKIs

Patients with Relapsed/Refractory Ph Negative ALL

Tisagenlecleucel is also an option for patients up to age 25 years of age < 26 years and with refractory disease or ≥ 2 relapses

*CAR T-cell therapy-associated TOXicity (CARTOX) Working Group* 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)* recently published the guideline called 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 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)* published a final Evidence Report (March 2018) entitled Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value. ICER's analyses reviewed outcomes for tisagenlecleucel in B-ALL and NHL and axicabtagene ciloleucel in NHL compared to outcomes in patients who received other therapies with similar FDA indications. Evidence is insufficient to judge whether one CAR-T therapy is superior 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, at the current time there is uncertainty given that the studies of CAR-T therapies are all single-arm trials that are small and have short follow-up. These uncertainties make the comparative efficacy analyses versus standard therapy controversial.

## DEFINITIONS

**ECOG (Eastern Cooperative Oncology Group)** Performance Status: A scale used to determine the individual's level of functioning; this scale may also be referred to as the WHO (World Health Organization) or Zubrod score; based on the following scale:

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 house work, 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

**Relapsed disease** is defined as the reappearance of leukemia cells in the bone marrow or peripheral blood after the attainment of a complete remission with chemotherapy and/or stem cell transplant.

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

## APPENDIX

Black box warnings from the FDA PI Label (2018) include the following information and recommendations:

- Cytokine release syndrome (CRS), including fatal or life-threatening reactions, occurred in individuals who received tisagenlecleucel; therefore, it should not be administered to anyone with an active infection or inflammatory disorders. Severe or life-threatening CRS should be treated with tocilizumab (Actemra, Genentech, Inc., Roche USA, South San Francisco, CA).
- Neurological toxicities, which may be severe or life-threatening, can occur following treatment with tisagenlecleucel; recipients should be carefully monitored for neurologic toxicity.
- Tisagenlecleucel is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIAH REMS.

Additional warnings from the FDA PI Label (2018) include the following information and recommendations:

- Secondary malignancies: Individuals treated with tisagenlecleucel may develop secondary malignancies or recurrence of their leukemia and should be monitored for life-long secondary malignancies.
- Hypersensitivity reactions: Serious hypersensitivity reactions, including anaphylaxis.
- Infections and febrile neutropenia: Serious infections, including life-threatening or fatal infections, occurred in individuals after tisagenlecleucel infusion.
- Prolonged cytopenias: Cytopenia may persist for several weeks following lymphodepleting chemotherapy and tisagenlecleucel infusion. Myeloid growth factors, particularly GM-CSF, are not recommended during the first 3 weeks after infusion or until CRS has resolved.
- Hypogammaglobulinemia: Hypogammaglobulinemia and agammaglobulinemia (IgG) can occur in individuals treated with tisagenlecleucel who achieve a CR. Recipients' immunoglobulin levels should be monitored after treatment and managed using infection precautions, antibiotic prophylaxis and immunoglobulin replacement standard guidelines.
- Vaccine administration: The safety of immunization with live viral vaccines during or following tisagenlecleucel treatment has not been studied; therefore, vaccination with live virus vaccines is not recommended for at least 2 weeks prior to the start of lymphodepleting chemotherapy, during tisagenlecleucel treatment, and until immune recovery following treatment.

**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** |
|---|---|
| J3490 | Unclassified drugs (when used to specify Kymriah or Yescarta) |
| J3590 | Unclassified biologics (when used to specify Kymriah or Yescarta) |
| Q2040 | Tisagenlecleucel, up to 250 million car-positive viable t cells, including leukapheresis and dose preparation procedures, per infusion (kymriah) [2018 code] |
| Q2042 | Tisagenlecleucel, up to 600 million CAR-positive viable T cells, including leukapheresis and dose preparation procedures, per therapeutic dose |
| **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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- Kymriah (Tisagenlecleucel) for Diffuse Large B-Cell Lymphoma. Jan, 2018.

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AMR Peer Review: Policy was reviewed by practicing physician board certified in Internal Medicine, Oncology, Hematology, 11/21/2017

AMR Peer Review: Policy was reviewed by practicing physician board certified in Internal Medicine, Oncology, Hematology, 1/28/2019

**Review/Revision History:**

4/12/2018: Policy created

3/11/2019: Policy revised.

- Previous policy (MCP-317) included both Kymriah and Yescarta; created individual policy for Kymriah (MCP-317a) and Yescarta (MCP-317b)
- 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.