Subject: CAR T-cell Therapy: Adoptive Immunotherapy Using Genetically Modified Lymphocytes for Lymphoproliferative Disorders and Hematological Malignancies [Kymriah and Yescarta]	Original Effective Date: 4/12/2018
Molina Clinical Policy (MCP) Number: MCP-317	**Revision Date(s):**
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DISCLAIMER

This Molina clinical policy 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 Molina clinical policy document and provide the directive for all Medicare members.[1]

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL [2-3 25-26]

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.

Examples of CAR T therapy include but may not be limited to the following:

- Kymriah (tisagenlecleucel, Novartis) is a CAR T cellular product that received FDA approval on August 30, 2017, 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. The Kymriah product label carries a boxed warning regarding risk of cytokine release syndrome (CRS), including fatal or life-threatening reactions, in patients receiving the therapy. It also warns of risk of severe or life-threatening neurological toxicities. Of note, the FDA on August 30, 2017, expanded indications for Actemra (tocilizumab) to include the treatment of CAR T-cell–induced severe or life-threatening CRS in patients 2 years of age or older. One treatment course consists of lymphodepleting chemotherapy followed by a single infusion of Kymriah.
- Yescarta (Axicabtagene Ciloleucel, Kite Pharma) is the second CAR T-cell therapy product to receive FDA approval on October 18, 2017. Yescarta is indicated to treat adult patients with relapsed or refractory large B-cell

lymphoma (after two or more lines of systemic therapy), including DLBCL not otherwise specified, PMBCL, high-grade B-cell lymphoma, and TFL. Yescarta is not indicated for the treatment of patients with primary central nervous system lymphoma. The Yescarta product label carries a boxed warning regarding risk of cytokine release syndrome (CRS), including fatal or life-threatening reactions, in patients receiving the therapy. It also warns of risk of severe or life-threatening neurological toxicities. One treatment course consists of lymphodepleting chemotherapy followed by a single infusion of Yescarta.

RECOMMENDATION [2-3 8-24]

Kymriah and Yescarta are available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the REMS. CAR-Tcell therapy must be performed at a certified healthcare facility that has enrolled in the REMS and training has been given to providers on the management of cytokine release syndrome (CRS) and neurological toxicities. Healthcare facilities certified to dispense and administer Kymriah and Yescarta must:

- Have on-site, immediate access to tocilizumab and ensure that a minimum of 2 doses of tocilizumab are available for each patient for administration within 2 hours after infusion, if needed for treatment of CRS.
- Ensure that healthcare providers who prescribe, dispense, or administer Kymriah and Yescarta are trained about 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.

1. **Kymriah** (Tisagenlecleucel) may be considered medically necessary when all of the following criteria are met:
    - ❑ Children and adolescents who are age 3 to 25 years; and
    - ❑ Prescribed by or in consultation with an oncologist; and
    - ❑ Documentation including full history and physical; and
    - ❑ Diagnosis B-cell precursor acute lymphoblastic leukemia (ALL); and
    - ❑ Patient has CD19-positive disease; and
        - o disease is refractory or in second or later relapse defined as one of the following: [ONE]
            - ➢ Second or greater bone marrow (BM) relapse; or
            - ➢ Any BM relapse after allogeneic stem cell transplantation (SCT); or
            - ➢ Primary refractory (not achieving a complete response after 2 cycles of standard chemotherapy) or chemorefractory (not achieving a complete response after 1 cycle of standard chemotherapy for relapsed disease); or
            - ➢ Patients with Philadelphia chromosome (Ph)-positive disease have a contraindication, intolerance, or have failed two prior lines of tyrosine kinase inhibitor (TKI) therapy (e.g., imatinib, dasatinib, ponatinib, etc.); and
    - ❑ Absence of active infection (including TB, HBV, HCV, and HIV); and
    - ❑ Patient has a performance status (Karnofsky/Lansky) ≥ 50; or Eastern Cooperative Oncology Group (ECOG) performance score is 0-3; and
    - ❑ Patient has not received prior CAR-T therapy; and
        - o One treatment course consists of lymphodepleting chemotherapy [Fludarabine (30 mg/m2 intravenous daily for 4 days) and cyclophosphamide (500 mg/m2 intravenous daily for 2 days starting with the first dose of fludarabine within two weeks preceding Kymriah infusion], followed by a single infusion of Kymriah and the dose is:
            - ➢ Weight ≤ 50 kg: administer 0.2 to 5.0 x 106 CAR-positive viable T cells per kg body weight
            - ➢ Weight > 50 kg: administer 0.1 to 2.5 x 108 CAR-positive viable T cells with a maximum of no more than 2.5 x 108 CAR-positive viable T cells

2. **Yescarta** (Axicabtagene Ciloleucel) may be considered medically necessary when all of the following criteria are met: [ALL]
    - ❑ Adults who are age 18 years or older; and
    - ❑ Prescribed by or in consultation with an oncologist; and
    - ❑ Documentation including full history and physical; and
    - ❑ Diagnosis of any of the following: [ONE]
        - o relapsed or refractory large B-cell lymphoma; or
        - o diffuse large B-cell lymphoma (DLBCL); or
        - o primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, or
        - o DLBCL arising from follicular lymphoma; AND
    - ❑ Relapsed or refractory disease, defined as one or more of the following: [ONE]
        - o No response to first (primary refractory disease), second or greater lines of therapy;
        - o Relapsed after autologous hematopoietic stem cell transplantation (HSCT);
        - o Relapsed transplant ineligible disease; AND
    - ❑ Must have received adequate prior therapy including at a minimum both of the following:
        - o Anti-CD20 monoclonal antibody (unless tumor is CD20 negative);
        - o An anthracycline containing chemotherapy regimen; AND
    - ❑ ALL of the following clinical findings: [ALL]
        - o Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and
        - o Absolute neutrophil count (ANC) ≥ 1000/uL; and
        - o Absolute lymphocyte count (ALC) > 100/uL; and
        - o Platelet count ≥ 75,000/uL; AND
        - o Absence of active infection (including TB, HBV, HCV, and HIV)
    - ❑ Chemotherapy refractive disease including prior treatment with an adequate chemotherapy regimen; and
    - ❑ Patient has not received prior CAR-T therapy; AND
        - o One treatment course consists of lymphodepleting chemotherapy [cyclophosphamide 500 mg/m2 intravenously and fludarabine 30 mg/m2 intravenously on the fifth, fourth, and third day before infusion of Yescarta; AND
        - o Dose is 2 × 106 CAR-positive viable T cells per kg body weight, with a maximum of 2 × 108 CAR-positive viable T cells

CONTINUATION OF THERAPY [2-3 8-24]

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 considered not medically necessary.

EXCLUSIONS [2-3]

- ❑ Pregnancy: There are no available data with Kymriah and Yescarta use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with Kymriah or Yescarta to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known if Kymriah or Yescarta have the potential to be transferred to the fetus. Therefore, Kymriah and Yescarta are excluded in pregnancy.
- ❑ Pediatric patients: The safety and efficacy of Yescarta have been established in pediatric patients; therefore Yescarta is excluded in the pediatric population. Clinical studies of Kymriah included patients who were 3 years of age to 25 years of age; therefore Kymriah is excluded in children who are younger than age 3 years.
- ❑ Geriatric patients: The safety and effectiveness of Kymriah and Yescarta have not been established in geriatric patients. Clinical studies of Kymriah and Yescarta for this indication did not include patients age 65 years and over.

- ❑ For all other indications not described in the clinical criteria section above that include but are not limited to:
  - Yescarta is not indicated for the treatment of patients with primary central nervous system lymphoma.

SUMMARY OF MEDICAL EVIDENCE [8-24]

Kymriah:

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). [23] Also published is a report on outcomes in patients who were treated in 2 phase I pilot trials (Maude et al., 2014). [12]

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. 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 CR or 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. [23]

Maude et al., 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.). [12]

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%. [13]

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. [14]

Yescarta

The best available published evidence on Yescarta for relapsed or refractory DLBCL is the phase II pivotal ZUMA-1 trial (Neelapu et al., 2017). [24] Also published are outcomes in 7 patients who participated in the phase I segment of the ZUMA-1 trial (Locke et al., 2017). [10] A report on outcomes in 7 patients with chemotherapy-refractory DLBCL treated with the same CAR T-cell therapy construct as Yescarta (but manufactured differently) is also published (Kochenderfer et al., 2015). [11]

Phase I ZUMA-1 trial (Locke et al., 2017): In the multicenter ZUMA-1 phase 1 study, KTE-C19, an autologous CD3ζ/CD28-based chimeric antigen receptor (CAR) T cell therapy, was evaluated in patients with refractory DLBCL. Patients received low-dose conditioning chemotherapy with concurrent cyclophosphamide (500 mg/m2) and fludarabine (30 mg/m2) for 3 days followed by KTE-C19 at a target dose of 2 × 106 CAR T cells/kg. The incidence of dose-limiting toxicity (DLT) was the primary endpoint. Seven patients were treated with KTE-C19 and one patient experienced a DLT of grade 4 cytokine release syndrome (CRS) and neurotoxicity. Grade ≥3 CRS and neurotoxicity were observed in 14% (n = 1/7) and 57% (n = 4/7) of patients, respectively. All other KTE-C19-related grade ≥3 events resolved within 1 month. The overall response rate was 71% (n = 5/7) and complete response (CR) rate was 57% (n = 4/7). Three patients have ongoing CR (all at 12+ months). CAR T cells demonstrated peak expansion within 2 weeks and continued to be detectable at 12+ months in patients with ongoing CR. This regimen of KTE-C19 was safe for further study in phase 2 and induced durable remissions in patients with refractory DLBCL.[10]

ZUMA-1 Trial (Neelapu et al., 2017): This multicenter trial enrolled 111 patients with refractory DLBCL, PMBCL or TFL. A total of 101 patients were treated with Yescarta, including 77 patients with DLBCL, 8 patients with PMBCL, and 16 patients with TFL. Yescarta was not successfully manufactured for 1 of the 10 patients not treated; other reasons for nontreatment included an adverse event prior to Yescarta infusion (n=4), death from disease progression (n=1),

nonmeasurable disease (n=2), sepsis (n=1), and death from presumed tumor lysis syndrome (n=1). The median age of the study population was 58 years; 85% had stage III or IV disease, 21% had disease relapse within 12 months of ASCT, and 69% had a history of ≥ 3 prior lines of therapy. All patients received a conditioning regimen of cyclophosphamide at 500 mg/m2 and fludarabine at 30 mg/m2, followed by a single infusion of Yescarta at a target dose of 2×106 cells/kg of body weight. Patients who had an initial response and then had disease progression at least 3 months after the first dose of Yescarta could be retreated. The median turnaround time for production of Yescarta was 17 days. The primary efficacy endpoint was objective response rate (partial and complete combined), as assessed when 92 patients could be evaluated 6 months after Yescarta infusion. This endpoint was compared with a preset historical objective response rate of 20%, which was based rates reported in the literature for refractory DLBCL. At a minimum of 6 months follow-up, the objective response rate was 82%, which was significantly superior to the historical objective response rate (P<0.001). Among these patients, the overall complete response rate was 52%, with 47% of patients with DLBCL and 70% of patients with either PMBCL or TFL achieving a complete response. The median time to response was 1 month (range, 0.8 to 6.0) and the median duration of response was 8.1 months. CRS of any grade occurred in 95% of treated patients; grade 1 or 2 CRS was reported in 80% of patients, and 13% of patients had grade ≥ 3 CRS. Three patients died during treatment; 2 deaths were related to Yescarta. Included in this published report is an updated analysis of outcomes in 108 patients who participated in the phase I and II segments of the ZUMA-1 trial. At a minimum 1 year follow-up, the objective response rate remained 82%; the complete response rate was 58%. Progression-free survival rates (secondary endpoint) in this updated analysis were 44% at 12 months and 41% at 15 months. The median overall survival had not yet been reached. [24]

Kochenderfer et al., 2015: The safety and efficacy of administering autologous anti-CD19 CAR T cells to patients with advanced CD19(+) B-cell malignancies was assessed in 15 patients with advanced B-cell malignancies. Nine patients had diffuse large B-cell lymphoma (DLBCL), two had indolent lymphomas, and four had chronic lymphocytic leukemia. Patients received a conditioning chemotherapy regimen of cyclophosphamide and fludarabine followed by a single infusion of anti-CD19 CAR T cells. The results showed that of 15 patients, eight achieved complete remissions (CRs), four achieved partial remissions, one had stable lymphoma, and two were not evaluable for response. CRs were obtained by four of seven evaluable patients with chemotherapy-refractory DLBCL; three of these four CRs are ongoing, with durations ranging from 9 to 22 months. Acute toxicities including fever, hypotension, delirium, and other neurologic toxicities occurred in some patients after infusion of anti-CD19 CAR T cells; these toxicities resolved within 3 weeks after cell infusion. One patient died suddenly as a result of an unknown cause 16 days after cell infusion. CAR T cells were detected in the blood of patients at peak levels, ranging from nine to 777 CAR-positive T cells/μL. The report concluded that these results demonstrate the feasibility and effectiveness of treating chemotherapy-refractory B-cell malignancies with anti-CD19 CAR T cells. The numerous remissions obtained provide strong support for further development of this approach. [11]

CAR-T Therapy Systematic Reviews/Meta-Analyses

Holzinger et al., 2016: A meta-analysis evaluated CAR T cells targeted toward CD19 for B-cell malignances. Fourteen clinical trials including 119 patients were included for analysis. The authors calculated an overall pooled response rate of 73% (95% CI, 46%-94%) and noted significant heterogeneity across studies (P<0.001). Patients with ALL were found to have higher response rates than those with chronic lymphocytic leukemia or lymphoma (93% versus 62% and 36%). Some factors associated with improved responses included a lymphodepletion regimen and not using interleukin-2 to stimulate the cells (Zhang et al., 2015). In a 2016 comprehensive and notable narrative review, Holtzinger et al. (2016) list over 100 ongoing clinical trials evaluating CAR T cells with a variety of targets for a variety of indications. They note that the majority of trials are underway in the United States or Canada, and about a quarter of the trials are underway in China. They also briefly review 7 completed phase I trials on CAR T cells for hematological malignancy. The authors conclude that more research is needed to identify ideal CAR T cell targets, receptor designs, and lymphodepletion regimens; control toxic effects like CRS; and evaluate the use of CAR T cells with HSCT. [15]

Professional Society Guidelines:

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 multiorgan 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. [4]

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. [5]

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.[7]

The National Comprehensive Cancer Network (NCCN) guideline for Acute Lymphoblastic Leukemia (version 5.2017) recommends Kymriah as a treatment option for patients < 26 years of age with refractory disease or ≥ 2 relapses. The guideline on DLBCL (version 7.2017), released in January 2018, includes Yescarta as an option for the treatment of relapsed/refractory DLBCL (after 2 or more lines of systemic therapy). [8]

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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]
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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26. Hayes Directory Report. Adoptive Immunotherapy using Genetically Modified Lymphocytes for Lymphoproliferative Disorders or Hematological Malignancies. Winifred Hayes Inc. Lansdale, PA.September, 2017.
27. AMR Peer Review: Policy was reviewed by practicing physician board certified in Internal Medicine, Oncology, Hematology, 11/21/2017

Review/Revision History:

4/12/18: Policy created