Kymriah (Tisagenlecleucel)*

Medical Policy #: 08.01.30
Original Effective Date: October 2018
Reviewed: October 2022
Revised: October 2020

NOTICE: This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations, or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This medical policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

This Medical Policy document describes the status of medical technology at the time the document was developed. Since that time, new technology may have emerged, or new medical literature may have been published. This Medical Policy will be reviewed regularly and be updated as scientific and medical literature becomes available; therefore, policies are subject to change without notice.

DESCRIPTION

Kymriah™ (tisagenlecleucel) is a genetically modified autologous cellular immunotherapy comprised of chimeric antigen receptor (CAR) T-cells specific to CD19, a cell surface protein found on normal and malignant B-cells. It is a customized treatment that is prepared using an individual patient's own T-cells. Steps for preparing Kymriah (tisagenlecleucel) include collecting a patient's immune cells from blood via leukapheresis; sending the cells to a manufacturing facility; genetically modifying the patient's T-cells to produce CD19-specific CARs on their surface; expanding the number of CAR T-cells; returning the cells to the treatment facility; and infusing the CAR T-cells back into the patient. This process takes about 2 weeks. Patients typically receive lymphodepleting chemotherapy (cyclophosphamide and fludarabine) prior to intravenous infusion of Kymriah (tisagenlecleucel).

Kymriah (tisagenlecleucel) is a CD19-directed genetically modified autologous T-cell immunotherapy which involves reprogramming a patient's own T-cells with a transgene coding a chimeric antigen receptor (CAR) to identify and eliminate CD19-expressing malignant and normal cells. The CAR is comprised of a murine single-chain antibody

fragment which recognizes CD19 and is fused to intracellular signaling domains from 4-IBB (CD137) and CD3 zeta. The CD3 zeta component is critical for initiating T-cell activation and antitumor activity, while 4-1BB enhances the expansion and persistence of Kymriah (tisagenlecleucel). Upon unbinding to CD19-expressing cells, the CAR transmits a signal to promote T-cell expansion, activation, target cell elimination, and persistence of the Kymriah cells.

Severe and life-threatening adverse reactions have occurred in patients receiving Kymriah (tisagenlecleucel), including cytokine release syndrome (CRS) and neurological toxicities. Due to these safety concerns, the FDA regulates Kymriah (tisagenlecleucel) through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the Kymriah REMS. Under the REMS, only certified healthcare facilities can administer Kymriah (tisagenlecleucel). The prescribing information for Kymriah (tisagenlecleucel) also includes a black box warning. The required components of REMS are:

- Healthcare facilities that dispense and administer CAR-T cell therapy Kymriah must be enrolled and comply with REMS requirements. Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of two doses of tocilizumab are available for each patient for infusion within 2 hours after Kymriah, if needed for treatment of CRS.
- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer Kymriah are trained about the management of cytokine release syndrome (CRS) and neurological toxicities.

Kymriah (Tisagenlecleucel) is currently FDA approved for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse; and for the treatment of adult patients with relapsed and refractory large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DCBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma. Kymriah is not indicated for the treatment of patients with primary central nervous system lymphoma.

Kymriah (Tisagenlecleucel) for B-Cell Acute Lymphoblastic Leukemia (ALL)
Acute lymphoblastic leukemia (ALL) is a malignancy (clonal) of the bone marrow in which the early lymphoid precursors of the white blood cells (called lymphoblasts) proliferate and replace the normal hematopoietic cells of the marrow. This results in overcrowding of the bone marrow, as well as the peripheral organs (particularly the liver, spleen, and lymph nodes) by the lymphoblasts. As a consequence, the leukemic blasts displace the normal hematopoietic bone marrow and cause cytopenias in all 3 cell lineages (anemia, thrombocytopenia, granulocytopenia). Leukostasis affecting brain and lung may also occur. Death occurs commonly due to severe pancytopenia and resulting infections.

The age adjusted incidence rate of ALL 1.8 per 100,000 individuals per year, with approximately 6,660 new cases and 1,560 deaths estimated in 2022. The median age at diagnosis for ALL is 17 years with 53.5% of patients diagnosed at younger than 20 years of age. In contrast, 29.6% of cases are diagnosed at 45 years or older and only approximately 13.7% of patients are diagnosed at 65 years or older. ALL represents 75% to 80% of acute leukemias among children, making it the most common form of childhood leukemia; by contrast, ALL represents approximately 20% of the leukemias among adults.

The clinical presentation of ALL is typically nonspecific, and may include fatigue or lethargy, constitutional symptoms (e.g., fevers, night sweats, weight loss), dyspnea, dizziness, infections, and easy bruising or bleeding. Among children, pain the in the extremities or joints may be the only presenting symptom. The presence of lymphadenopathy, splenomegaly, and/or hepatomegaly on physical examination may be found in approximately 20% of patients. Abdominal masses from gastrointestinal involvement, or chin numbness resulting from cranial nerve involvement, are more suggestive of mature B-cell ALL.

Diagnosis of ALL generally requires demonstration of 20% or greater bone marrow lymphoblasts on hematopathology review of bone marrow aspirate and biopsy materials. Various disease-related and patient specific factors may have prognostic significance in patients with ALL. In particular patient age, WBC count, immunophenotypic/cytogenetic subtype, presence of CNS disease, and response to induction therapy have been identified as important factors in defining risk and assessing prognosis for both adult and childhood ALL.

- **Ph- Positive ALL**: Ph- positive ALL is rare in children with ALL, occurring in only approximately 3% of pediatric cases compared with 25% of adult cases. The frequency of Ph- positive ALL among adolescents and young adult (AYA) patients ranges from 5% to 25% and increases with age, although this subtype is still uncommon relative to the incidence in older adults. Historically, children and adolescents with Ph- positive disease had a poorer prognosis compared with patients with Ph negative B-cell ALL. However, recent improvements in the treatment options are closing this gap.
- **Ph- Negative ALL**: Despite major advances in the treatment of childhood ALL, approximately 20% of pediatric patients experience relapse after initial CR (complete remission) to frontline treatment regimens. Among those who experience relapse, only approximately 30% experience long-term remission with subsequent therapies.

The treatment approach to ALL represents one of the most complex and intensive programs in cancer therapy. Although the specific treatment regimens and selection of drugs, dose schedules, and treatment durations differ between AYA patients and adults, and among different subtypes of ALL, the basic treatment principles are similar. The most common treatment regimens used in patients with ALL include modifications or variations of multiagent chemotherapy regimens. In general, the treatment phases can be

largely grouped into induction, consolidation, and maintenance. All treatment regimens for ALL include CNS prophylaxis and/or treatment.

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).

Relapsed disease describes the reappearance of leukemia cells in the bone marrow or peripheral blood after the attainment of a complete remission. Minimal residual disease (MRD) refers to the presence of disease in cases deemed to be in complete remission by conventional pathologic analysis. MRD positivity is defined as the presence of 0.01% or more ALL cells and has been shown to be a strongest prognostic factor to predict the risk of relapse and death when measured during and after induction therapy in both newly diagnosed and relapsed ALL. The treatment of patients who experience relapse after initial therapy for ALL remains a challenge, because these patients have a very poor prognosis.

Currently bone marrow transplant is the only cure for refractory or relapsed ALL, but many patients are not eligible for transplant based on age or progression of the disease. The generation of chimeric antigen receptor (CAR) T-cells to treat B-cell ALL represents a significant advance in the field and has shown significantly greater OS (overall survival) than current regimens. CAR-T cell therapy Kymriah (Tisagenlecleucel) was recommended for accelerated approval by the FDA oncologic drug advisory committee in July 2017 and fully approved by the FDA in August 2017 for the treatment of patients up through age 25 years with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

Clinical Context and Therapy Purpose
The purpose of Kymriah (tisagenlecleucel) is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients who are up to 25 years of age with relapsed or refractory B-cell acute lymphoblastic leukemia (ALL).

Populations
The relevant population of interest is individuals who are up to 25 years of age with relapsed or refractory CD19-positive B-cell ALL. Relapsed disease describes the reappearance of leukemia cells in the bone marrow or peripheral blood after the attainment of a complete remission with chemotherapy and/or allogeneic cell transplant. Refractory (resistant) disease is defined as those patients who fail to obtain a 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).

Interventions
The therapy being considered is Kymriah (tisagenlecleucel). Therapy with Kymriah (tisagenlecleucel) involves patient apheresis for harvesting of cells to be utilized for autologous T-cell expansion, manufacturing of CAR-positive T-cells, patient completion of a lymphodepleting chemotherapy regimen, and intravenous infusion of Kymriah (tisagenlecleucel) at a body weight-dependent target dose.

Comparators
In general, the only curative therapy for relapsed or refractory ALL is allogeneic hematopoietic cell transplantation (HCT). The primary goal in patients who have relapsed, or refractory disease is achievement of complete remission or sufficient cytoreduction to enable allogeneic HCT. The choice of remission induction therapy depends on the disease subtype and clinical characteristics and includes participation in a clinical trial, immunotherapeutic approaches (e.g., blinatumomab, inotuzumab ozogamicin, CAR T-cell therapy) or chemotherapy regimens. All options have a category 2A recommendation in the National Comprehensive Cancer Network (NCCN) guidelines.

Outcomes
The general outcomes of interest are overall survival (OS), disease-specific survival (DSS), quality of life (QOL), treatment-related mortality, and treatment-related morbidity. Follow-up at 15 years is of interest for Kymriah (tisagenlecleucel) to monitor relevant outcomes.

Objective or overall response rates are typically calculated as the sum of patients achieving complete response (CR) and CR with incomplete blood count recovery. Partial response (PR) is not defined for this disease. Response criteria utilizing conventional morphological features are published by the NCCN.

A minimal residual disease (MRD) can also be calculated for patients. Minimal residual disease refers to the presence of leukemic cells below the limit of detection by conventional morphologic and cytogenetic methods. Patients who achieve a CR by morphologic assessment alone can potentially harbor a significant number of leukemic cells in the bone marrow, and this has been shown to contribute to risk of future relapse. Regular MRD monitoring is consider an essential component of patient evaluation. Flow cytometry or polymerase chain reaction (PCR) methods are recommended for MRD monitoring. Minimal residual disease positivity is defined as the presence of 0.01% or more ALL cells and has been shown to be the strongest prognostic factor to predict the risk of relapse and death when measured during and after induction therapy in both newly diagnosed and relapsed ALL. In a meta-analysis of 20 studies of pediatric ALL (N = 11,249), Berry et al (2017) reported a hazard ratio for event-free survival in MRD-negative patients compared with MRD-positive patients of 0.23 (95% confidence interval [CI], 0.18 to 0.28). Event-free survival in the context of CAR-T therapy is typically defined as the date of infusion to the date of treatment failure (e.g., relapse, development of a second neoplasm, or death in remission).

Cytokine release syndrome (CRS) and neurologic toxicity, also known as CAR-T-related encephalopathy syndrome, are 2 significant CAR-T therapy-mediated adverse events that contribute to treatment-related morbidity and mortality outcomes. Cytokine release syndrome manifests with a variety of symptoms, including fever, organ toxicity, hypotension, and hypoxia, and may be life-threatening. Several grading scales have been used to rate CRS. However, consensus criteria published by the American Society for Transplantation and Cellular Therapy (ASTCT) is preferred to grade CAR-T therapy-mediated CRS and neurotoxicity.

Pivotal Trial

In the pivotal trial phase 2 single-arm, international, multicenter trial (study B2202), 68 patients ages 3 to 21 years at screening, with CD19-positive second or greater bone marrow relapse or primary refractory B-cell acute lymphoblastic leukemia were treated with Kymriah (tisagenlecleucel) and followed for 12 months. This trial has not been published; information was obtained from the Food and Drug Administration Oncologic Drugs Advisory Committee Meeting held in July 2017. Sixty-three patients received U.S.-manufactured product while 5 patients received EU-manufactured product. Patients were required to have more than 5% blasts at screening and either ineligible for, or have relapsed after, allogeneic cell transplant. Refractory was defined by not achieving an initial CR after 2 cycles of a standard chemotherapy regimen (primary refractory). Subjects who were refractory to subsequent chemotherapy regimens after an initial remission were considered chemo-refractory.

The prespecified primary efficacy end point was the proportion of patient who achieved objective remission rate (ORR; CR or CR with incomplete blood count recovery [CRi]) as assessed by an independent review committee within 3 months after Kymriah (tisagenlecleucel) infusion. The trial would meet its primary objective if the lower bound of the 2-sided 95% confidence intervals for ORR was greater than 20%. The key secondary outcome was proportion of patients who achieve best ORR (CR or CRi with an minimal residual disease [MRD]–negative bone marrow) within 3 months of receiving Kymriah (tisagenlecleucel). Key secondary end points were tested sequentially (after primary end point was significant) to control for overall type I error.

Of 107 patients who were screened, 88 met the trial inclusion criteria and of these 68 (77.3%) were infused with Kymriah (tisagenlecleucel). In 7 (8%) patients, Kymriah (tisagenlecleucel) could not be manufactured. The median time from enrollment to infusion was 44 days. Of the 68 patients, 63 patients received Kymriah (tisagenlecleucel) infusion at least 3 months prior to the data cutoff date. Patients received investigator choice bridging chemotherapy as needed to control their leukemia while waiting for Kymriah (tisagenlecleucel) infusion. Patients also received protocol mandated lymphocyte-depleting chemotherapy 2 to 14 days prior to Kymriah (tisagenlecleucel) infusion. The median age was 12 years (range, 3-23 years), 82% were male, 75% were white, median Karnofsky/Lansky Performance Status score was 90 (range, 50-100), 79% had relapsed disease, 12% had chemo-refractory disease, and 9% had primary refractory disease. The enrolled patient population was heavily pretreated as evident by the

following statistics: 87% (59) of patients had received a prior hematopoietic cell transplant with a median of 3 previous treatments. Results summarized in Table 1 show that 52 (82.5%) patients who received Kymriah (tisagenlecleucel) infusion achieved a CR or CRi within 3 months. Of the 52 patients who achieved a CR or CRi within 3 months, 29 (56%) were still in remission,13 (25%) had relapsed, 12 (23%) were censored prior to the data cutoff. The reasons for censoring were six received hematopoietic cell transplant, five received a new cancer therapy, and one was lost to follow-up. The estimated relapse-free rate among responders at month 6 was 75.4% (95% CI, 57.2% to 86.7%). Among the responders, four died (three after disease relapse, one after new cancer therapy was initiated while in remission).

Table 1. Summary of Efficacy Results in 63 Patients in the Pivotal Study

Outcomes	Results, n (%) (95% confidence interval) or %
Primary end point (3 mo)	
Objective remission rate (CR + CRi)	52 (82.5) (70.9 to 91.0)
CR	40 (63)
CRi	12 (19)
Not reported/unknown	11 (17.5)
Secondary end point (3 mo)	
Best objective remission rate (Cr + CRi with MRD-positive)	52 (82.5) (70.9 to 91.0)
Other secondary end points	
Median duration of remission	Not reached
Median event-free survival	Not reached
Percent relapse-free at 6 mo after remission	75
Percent survival at 6 mo	89
Percent survival at 9 mo	79
Percent survival at 12 mo	79

CR: complete remission; CRi: complete remission with incomplete blood count recovery; MRD: minimal residual disease.

Supportive Studies

Two single-arm studies that included a total of 84 patients were conducted using product manufactured at University of Pennsylvania cell and vaccine production facility. The first study was a phase 1/2 a single-center study in 55 patients enrolled between March 2012 and November 2015. The objective remission rate (ORR) (CR or CRi) was 95% (52/55), and best ORR (CR or CRi with MRD-negative bone marrow) was 89% (49/55). Median OS was 32.7 months (95% CI, 21.0 to inestimable). First pediatric patient treated in the study has been in remission for 5 years. The second study was a phase 2 multi-centric study that enrolled 29 patients between August 2014 and February 2016. The objective remission rate (ORR) (CR or CRi) was 69% (20/29).

Safety
Safety data included 68 patients (63 patients received who U.S.-manufactured product plus 5 patients who received EU-manufactured product) and is summarized in Tables 2 and 3. Cytokine release syndrome (CRS) was the most common serious life-threatening adverse event in the pivotal study and required aggressive supportive measures. One fatality due to CRS-related coagulopathy was observed in the pivotal study. Any grade CRS occurred in 78% (53/68) patients while 47% (32/68) experienced a grade 3 or 4 CRS. The severity of CRS was associated with high tumor burden of greater than 50% blasts in the bone marrow at screening. CRS occurred after a median of 3 days (range, 1-22 days) after Kymriah (tisagenlecleucel) infusion and lasted for a median duration of 8 days. CRS resulted in significant morbidity burden as indicated by intensive care unit admission (31 [46%]), ventilatory support (10 [15%]), dialysis (7 [10%]), hypotension (35 [51%]), and hypotension requiring high-dose vasopressor support (17 [25%]).

The next most important adverse event of Kymriah (tisagenlecleucel) was neurotoxicity such as encephalopathy and seizures. Any grade neurotoxicity was reported in 44% (30/68) patients, and grade 3 neurotoxicity was reported in 15% (10/68) patients. No cases of grade 4 neurotoxicity were reported. Although neurotoxicity was reversible with the use of optimal and best supportive care, the severity of these toxicities requires monitoring for airway protection.

The Food and Drug Administration also noted infection as a special adverse event of interest. In the first 8 weeks after infusion, 43% (29/68) of patients developed infection of which 24% (16/68) were grade 3 and 3% (2/68) were grade 4. Infection included gram-positive, gram-negative systemic infections, Clostridium difficile, candida, herpes simplex, and encephalitis due to herpesvirus 6. Three deaths occurring within 60 days and related to infection with herpesvirus 6, bacterial infection, and fungal sepsis was reported.

Other adverse events of special interest included prolonged cytopenia, cardiac disorders, and B-cell aplasia. Three patients experienced congestive heart failure that required treatment. Most patients in the pivotal trial had previously been treated with chemotherapy and radiotherapy that predisposed them to cardiotoxicity; it is an anticipated risk in the intended population that would receive treatment with Kymriah (tisagenlecleucel). Acquired hypogammaglobulinemia is an expected side effect of Kymriah (tisagenlecleucel) because it not only kills pre-B acute lymphoblastic leukemia cells but also normal B cells because they are CD19-positive. Patients in the trial were maintained on supplemental treatment with intravenous gamma globulin after Kymriah (tisagenlecleucel). It is unclear as to how long intravenous gamma globulin would be required.

Multiple design features of the Kymriah (tisagenlecleucel) retroviral vector such as minimal homology between packaging plasmids and vector sequences, segregation on 4 different DNA plasmids, deletion of HIV accessory genes, and use of “self-inactivating” vector design aim to reduce the risk the potential of replication competent virus

generation and insertional mutagenesis. However, the theoretical risk of formation of replication competent virus, their clonal growth or neoplastic transformation of transduced cells cannot be ruled out. If approved each vector batch and production cells will be tested for the presence of replication competent retrovirus. However, Novartis does not plan to collect patient samples for replication competent retrovirus testing. It is expected that over next 5 years, approximately 5000 patients may be enrolled in the first 5 years in a post-marketing registry that will follow-up patients up to 15 years after Kymriah (tisagenlecleucel) infusion.

Table 2. Summary of Serious Adverse Events (>5% Patients) in 68 Patients in the Pivotal Study

Serious Adverse Event[a]	Results, n (%)
Cytokine release syndrome	43 (63)
Febrile neutropenia	14 (21)
Hypotension	8 (12)
Acute kidney injury	5 (7)
Fever	5 (7)
Hypoxia	4 (6)

[a] Any adverse event that resulted in death or was life-threatening or required inpatient hospitalization or caused prolongation of existing hospitalization or resulted in persistent or significant disability/incapacity or was a congenital anomaly/birth defect, or required intervention to prevent permanent impairment or damage.

Table 3. Summary of Adverse Events of Special Interest in 68 Patients in the Pivotal Study

Adverse Events	Grade 3, n (%)[a]	Grade 4, n (%)[b]	All Grades, n (%)
Patients with at least 1 event	23 (34)	28 (41)	62 (91)
Cytokine release syndrome	14 (21)	18 (27)	53 (78)
Febrile neutropenia	23 (34)	2 (3)	25 (37)
Hematopoietic cytopenia not resolved by day 28	10 (15)	12 (18)	25 (37)
Infections	16 (24)	2 (3)	29 (43)
Transient neuropsychiatric events	10 (15)	0	30 (44)
Tumor lysis syndrome	3 (4)	0	3 (4)

[a] Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care.
[b] Life-threatening consequences: urgent intervention indicated.

Summary of Evidence
For individuals who are up to 25 years of age with relapsed or refractory B-cell acute lymphoblastic leukemia (ALL) who receive Kymriah (tisagenlecleucel), the evidence includes single-arm prospective studies. The pivotal single-arm trial reported an 83% response rate (measured by complete response or complete remission with incomplete blood count) in heavily pretreated patients. All patients who achieved a complete remission with incomplete blood count were also minimal residual disease negative, which is predictive of survival in acute lymphoblastic leukemia patients. After a median follow-up of 4.8 months, the median duration of response was not reached. The observed benefits seen with Kymriah (tisagenlecleucel) were offset by a high frequency and severity of adverse events. Cytokine release syndrome (CRS) was observed in more than half (63%) of the patients, and approximately 40% had an adverse event at grade 4 or higher. Long term follow-up and real-world evidence are required to assess the generalizability of Kymriah (tisagenlecleucel) efficacy and safety outside of the clinical trial setting. The evidence is sufficient to determine this technology results in a meaningful improvement in the net health outcomes.

Kymriah (Tisagenlecleucel) for Relapsed or Refractory Large B-Cell Lymphomas
Non-Hodgkin's lymphoma (NHL) is a type of cancer that originates in lymphoid tissue and can spread to other organs. Non-Hodgkin's lymphomas (NHL) are a heterogeneous group of lymphoproliferative disorders originating in B lymphocytes, T lymphocytes or natural killer cells. In 2022, an estimated 80,470 people will be diagnosed with NHL, this includes both adults and children, and there will be approximately 20,250 deaths due to this cancer.

NHL can be divided into two prognostic groups: indolent lymphomas and aggressive lymphomas.

- Indolent lymphomas: Grow slowly; considered low grade lymphomas
- Aggressive lymphomas: Grow at a faster rate; considered high grade lymphomas

Sometimes lymphoma changes from a slow growing type into a faster growing type, this is known as transformation. The transformed lymphoma must then be treated as a high - grade lymphoma.

Non-Hodgkin's lymphoma is called "high- grade" when the cells appear to be dividing quickly. These may be called aggressive lymphomas.

Diffuse large B-cell lymphoma (DLBCL) are the most common lymphoid neoplasms in adults, accounting for approximately 30% of NHLs diagnosed annually. Subtypes include primary mediastinal large B-cell lymphoma, high grade B cell lymphoma and diffuse large B-cell lymphoma (DLBCL) arising from follicular lymphoma (follicular lymphoma with histologic transformation to diffuse large B-cell Lymphoma).

- **Diffuse large B-cell lymphoma (DLBCL)/High- Grade B-cell Lymphoma:** The lymphoma cells look fairly large when seen with a microscope. DLBCL can affect people of any age. It usually starts as a quickly growing mass in the lymph node deep inside the body such as in the chest or abdomen, or in a lymph node

such as in the neck or axilla. It may also start in other areas such as the intestines, bones or even the brain or spinal cord. DLBCL tends to be fast growing (aggressive) lymphoma.

- **Diffuse large B-cell lymphoma (DLBCL) arising from follicular lymphoma – histological transformation to DLBCL**: In patients with follicular lymphoma, histological transformation to DLBCL is generally associated with a poor clinical outcome. Histological transformation to DCBCL occurs at an annual rate of approximately 3% for 15 years and the risk of transformation falls after that time, for reasons that remain unclear. Follicular lymphoma is the most common subtype of indolent NHL. Usually, this lymphoma occurs in many lymph nodes sites throughout the body, as well as in the bone marrow.

Defining Relapsed and Refractory Disease
Refractory (resistant) disease is suggested by a less than 50 percent decrease in lesion size with treatment in the absence of new lesion development. In contrast progressive disease usually manifests as the appearance of any new lesion, a 50 percent increase in the longest diameter of a previously identified lesion or new/recurrent involvement in the bone marrow. Relapsed disease reflects the appearance of any new lesion after attainment of an initial complete remission.

Refractory or progressive disease is identified during the post-treatment response evaluation. The majority of relapses occur during the first two years after completion of treatment. However, as many as 18 percent of relapses occur more than five years after initial treatment. Relapses are usually symptomatic and rarely identified solely based on routine imaging. Progressive or relapse can present with systemic B symptoms (i.e., fever, night sweats, weight loss), cytopenias, the development of an extranodal mass, or as the symptomatic or asymptomatic enlargement of the lymph nodes, liver or spleen.

When relapse is suspected, a biopsy of the involved lymph node or mass is recommended to confirm relapse and evaluate a potential change in histology, for example indolent non-Hodgkin’s lymphoma to an aggressive non-Hodgkin’s lymphoma.

Treatment for Relapsed or Refractory Disease
Outcomes for patients with refractory diffuse large B-cell lymphoma (DLBCL) are poor.

Relapse or refractory diffuse large B-cell lymphomas is treated with systemic chemotherapy with or without rituximab with plans to proceed to high dose chemotherapy and hematopoietic stem cell transplantation (HCT) in those with chemotherapy sensitive disease. The treatment of patients who are not candidates for HCT, who fail to respond to second-line chemotherapy regimens, or who relapse after HCT is generally palliative.

In the absence of HCT, conventional chemotherapy regimens provide only transient disease control for the majority of patients with relapsed or refractory disease. Patients with primary refractory disease rarely achieve complete remission when treated with a

second chemotherapy regimen. Following relapses from a first complete remission, a subset of patients will achieve a second complete remission with chemotherapy; however, these remissions are generally not durable, and long- term disease free survivors are rare. In contrast, approximately half of patients who respond to a second chemotherapy regimen and proceed to HCT will maintain their response for two years.

Kymriah™ (tisagenlecleucel) is now a treatment option for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma and DLBCL arising from follicular lymphoma (follicular lymphoma with histologic transformation to diffuse large B-cell lymphoma). Kymriah is not indicated in the treatment of patients with primary central nervous system lymphoma.

The current NCCN guideline B-Cell Lymphomas Version 5.2022 states the following: "Tisagenlecleucel is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL, NOS and high-grade B-cell lymphomas and DLBCL arising from follicular lymphoma."

Clinical Context and Therapy Purpose
The purpose of Kymriah (tisagenlecleucel) is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients who are adults with specific types of aggressive non-Hodgkin lymphoma (NHL).

Populations
The relevant population of interest is individuals who are adults with specific types of relapsed or refractory aggressive NHL. This includes diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and transformed follicular lymphoma. Relapsed or refractory disease is defined as disease progression after 2 or more lines of systemic therapy, which may or may not include therapy supported by autologous cell transplant.

Interventions
The therapy being considered is Kymriah (tisagenlecleucel).

Comparators
Treatment of relapsed/refractory cases is generally stratified according to HCT eligibility. There is general consensus that salvage therapy followed by autologous transplantation is the preferred treatment for medically eligible patients with a first relapse of DLBCL or primary refractory DLBCL. For patients who have chemoresistant disease (i.e., an inadequate response to salvage therapy) or relapse after autologous transplant, allogeneic HCT and CAR- T therapy are appropriate options. U.S. Food and Drug Administration (FDA) approved agents for refractory/relapsed DLBCL include pembrolizumab (Keytruda), polutuzumab vedotin-piiq (Polivy), selinexor (Xpovio), and tafasitamab-cxix (Monjuvi).

Outcomes
The general outcomes of interest are overall survival (OS), disease-specific survival (DSS), quality of life (QOL), treatment-related mortality, and treatment-related morbidity.

International Working Group response criteria for malignant lymphoma or Lugano criteria are used to assess response in patients with lymphoma. Responses are categorized as complete, partial, stable, or progressive. The primary endpoint in clinical trials is generally the proportion of patients with an objective response (complete or partial response) as assessed by an independent radiology review committee.

As mentioned in a previous section of this document, the severity of CAR-T therapy mediated CRS and neurologic toxicity is assessed by ASTCT criteria.

Pivotal Trial
The approval for Kymriah (tisagenlecleucel) for large B-cell lymphoma is supported by data from the 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). 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 $\geq$ 18 years of age with relapsed or refractory DLBCL, who receive $\geq$ 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 $\geq$ 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 $\leq$ 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 3.5×10^8 CAR-positive viable T cells (range 1.0 to 5.2×10^8 cells). Seventy-three percent of patients received Kymriah in the inpatient setting. Efficacy was established based on 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.

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.

Additional Indications for Kymriah (Tisagenlecleucel) for the following B-Cell Lymphoma Subtypes

The National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium (accessed October 2022) include the following category 2A recommendations for Kymriah (Tisagenlecleucel) in the following subtypes for B-cell lymphomas:

Treatment for relapsed AIDS-related diffuse large B-cell lymphoma, Primary effusion lymphoma and HHV8-positive diffuse large B-cell lymphoma, not otherwise specified (NOS) as:

- Additional therapy for patients with intention to proceed to transplant who have a partial response following second line therapy for relapsed or refractory disease; **or**
- Treatment (if 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.

Non-Hodgkin's lymphoma (NHL), Kaposi sarcoma (KS) and lung cancer are the most common cancer types diagnosed in people with human immunodeficiency virus (HIV) in the United States. Diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), and primary central nervous system lymphoma (PCNSL), are the most common subtypes of NHL in people living with HIV.

HHV8-positive diffuse large B-cell lymphoma, also called Kaposi sarcoma-associated herpesvirus or KSHV.

Treatment of monomorphic post-transplant lymphoproliferative disorders (PTLD) B-cell type as:

- Additional therapy for patients with intention to proceed to transplant who have partial response following second line chemoimmunotherapy for relapsed or refractory disease; or
- Treatment of disease in second relapse or greater (if not previously given).

Post-transplant lymphoproliferative disorders (PTLD) are a heterogenous group of lymphomas that occur after solid organ transplant (SOT) or allogeneic hematopoietic cell transplant (HCT) that are related to immunosuppression and the Epstein-Barr virus (EBV). PTLD following SOT are of recipient origin in the majority of cases, often involving the grafted organ, whereas PTLD following allogeneic HCT are usually donor origin.

The incidence of PTLD following SOT varies significantly depending on the transplanted organ (kidney transplant 0.8 to 2.5%; pancreatic transplants, 0.5% to 5% liver transplants; heart transplants 2.0% to 8%; lung transplants 3% to 10%, and multiorgan and intestinal transplants $\leq$ 20%). The incidence of PTLD following allogeneic HCT varies depending on the degree of human leucocyte antigen (HLA) matching and the need for T-cell depletion protocol prior to transplantation. Thus, the incidence of PTLD is the highest following haploidentical allogeneic HCT especially in cases of selective T-cell depletion

(> 20%) followed by cases of unrelated donors (4% to 10%); umbilical cord transplants (4% to 5%); and matched, related donors (1% to 3%).

There are six main types of PTLD based on World Health Organization (WHO). The type of PTLD is important in identifying treatment plans. Monomorphic PTLD is the most common subtype of PTLD, and the majority are of B-cell origin with diffuse large B-cell lymphoma (DLBCL) being the most frequent subtype.

B-Cell Lymphomas - Histologic Transformation of Nodal Marginal Zone Lymphoma to Diffuse Large B-Cell Lymphoma
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)

Marginal zone lymphomas (MZLs) originate in the marginal zone of lymphoid follicles found in the mucosa-associated lymphoid tissues (MALT), spleen and lymph nodes. Extranodal MZLs of MALT (MALT lymphomas), nodal MZL (NMZL), and splenic MZL (SMZL) are the three distinct subtypes of MZLs.

Summary of Evidence
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) and DLBCL subtypes. 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. The current NCCN guidelines recommend the use of Kymriah (tisagenlecleucel) in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and DLBCL subtypes. The evidence is sufficient to determine that the technology results in a meaningful improvement in net health outcomes.

Regimens for Relapsed or Refractory Ph-Negative B-ALL

- **Preferred Regimens**
  - Blinatumomab (for B-ALL only) (category 1)
  - Inotuzomab ozogamicin (for B-ALL only) (category 1)
  - Tisagenlecleucel (for B-ALL) (patients < 26 years and with refractory disease or ≥ 2 relapses)
  - Brexucabtagene autoleucel (for B-ALL only).

Regimens for Relapsed or Refractory Ph-Positive B-ALL

- **Other Recommended Regimens**
  - TKI (dasatinib, imatinib, ponatinib, nilotinib, or bosutinib)
    - The TKIs noted above may also be used in combination with any of the induction regimens noted on ALL-D1 or 10 that were not previously given.; or
  - Blinatumomab ±TKI
  - Inotuzumab ozogamicin ± TKI intolerant/refractory
  - Tisagenlecleucel (patients < 26 years and with refractory disease or ≥ 2 relapses and failure of 2 TKIs)
  - Brexucabtagene autoleucel (following therapy that has included TKIs)
  - The regimens listed on ALL-D 4 of 10 for Ph-negative B-ALL may be considered for Ph-positive B-ALL refractory to TKIs.

Evaluation and Treatment of Extramedullary Involvement

- CNS involvement should be evaluated (by LP) at the appropriate timing:
  - Timing of LP should be consistent with the chosen treatment regimen
  - Pediatric-inspired regimens typically include LP at the time of diagnostic workup
  - The panel recommends that LP be done concurrently with initial IT therapy
- Classification of CNS status:
  - CNS-1: No lymphoblasts in cerebrospinal fluid (CSF) regardless of white blood cell (WBC) count
  - CNS-2: WBC <5/mcL in CSF with presence of lymphoblasts
  - CNS-3: WBC ≥ 5/mcL in CSF with presence of lymphoblasts
- If the patient has leukemic cells in the peripheral blood and LP is traumatic and WBC ≥ 5/mcL in CSF with blasts, then compare the CSF WBC/red blood cell (RBC) ratio in the blood WBC/RBC ratio. If the CSF ratio is at least two-fold greater than the blood ratio, then the classification is CNS-3; if not then it is CNS-2.

CAR T Cells
Currently, bone marrow transplant is the only cure for R/R ALL; but many patients are not eligible for transplant based on age or progression of disease. The generation of chimeric antigen receptor (CAR) T cells to treat ALL represents a significant advance in the field and has shown significantly greater OS than current regimens. The pre-treatment of patients with CAR T cells has served as a bridge for transplant, and patients who were formerly unable to be transplanted due to poor remission status have a CR and ultimately transplantation. CAR T- cell therapy relies on the genetic manipulation of patients' T-cells to engender a response against a leukemic cell-surface antigen, most commonly CD19. CAR T-cell therapy/tisagenlecleucel was recommended for accelerated approval by the FDA oncologic drug advisory committee on July 2017 and fully approved by the FDA in August 2017 for the treatment of patients up to 25 years (aged <26 years) with R/R precursor B-cell ALL.

Patients with Relapsed/Refractory Ph- Positive B-ALL
For all patients with relapsed or refractory Ph- positive B-ALL, participation in a clinical trial is preferred. In the absence of an appropriate trial, patients may be considered for second-line therapy with an alternative TKI (i.e., different from the TKI used as part of induction therapy) alone, TKI combined with multiagent chemotherapy, or TKI combined with corticosteroids (especially for elderly patients who may not tolerate multiagent combination therapy). Blinatumomab with or without TKI may also be considered. For patients that are refractory or intolerant to TKIs, InO with or without bosutinib is recommended. Compared to standard care, InO is associated with increased hepatotoxicity, including fatal and life-threatening hepatic veno-occlusive disease, and increased risk of post-hematopoietic stem cell transplant (HSCT) non-relapse mortality. 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.

If transplant naïve patients experience a second complete remission (CR) prior to transplant, consolidative allogeneic HCT should be strongly considered. For patients with disease that relapses after an initial allogeneic HCT, other options may include a second allogeneic HCT and/or DLI (donor lymphocyte infusion). However, the role of allogeneic HCT following treatment with tisagenlecleucel is unclear. While persistence of tisagenlecleucel in peripheral blood and persistent B-cell aplasia has been associated with durable clinical responses without subsequent allogeneic HCT, further study will be required before conclusive recommendations can be made. For patients with Ph- positive ALL that is refractory to TKIs, regimens for relapsed or refractory Ph- negative ALL can be considered.

Patients with Relapsed/Refractory Ph- Negative B-ALL
For patients with R/R Ph- negative B-ALL, the approach to second-line treatment may depend on the duration of the initial response. For late relapses (i.e., relapses occurring ≥ 36 months from initial diagnosis), retreatment with the same induction regimen is a reasonable option. For other patients, participation in a clinical trial is preferred, when possible. In the absence of an appropriate trial, for patients with R/R Ph negative

precursor B-ALL, recommend category 1 options include blinatumomab or InO. As previously mentioned, InO is associated with increased hepatotoxicity, including fatal and life-threatening hepatic veno-occlusive disease and increased risk of post-HCST non-relapse mortality.

Tisagenlecleucel is also an option for patients up to age 25 years of age < 26 years and with refractory disease or ≥ 2 relapses. Other options that may be considered include subsequent chemotherapy, with regimens containing clofarabine, nelarabine (for T-cell ALL), VSLI, augmented hyper-CVAD, MopAD regimen, or other cytarabine or alkylator-containing regimens. If transplant naïve patients experience a second CR prior to transplant, consolidative allogeneic HCT should be strongly considered. For patients with disease that relapses after an initial allogenic HCT, other options may include a second allogeneic HCT and/or DLI. However, the role of allogeneic HCR following treatment with tisagenlecleucel is unclear. While persistence of tisagenlecleucel in the peripheral blood and persistent B-cell aplasia has been associated with durable clinical responses without subsequent allogeneic HCT, further study will be required before conclusive recommendations can be made.

Pediatric Acute Lymphoblastic Leukemia Version 1.2022

Principles of Systemic Therapy CD19-Targeting CAR T-Cell Therapy
Tisagenlecleucel

- The FDA label indication for use of tisagenlecleucel is for patients < 26 years of age and CD19+ B-ALL that is refractory or with ≥ 2 relapses. Of note, there has been limited published experience with the use of CAR T-cell therapy in infants < 12 months of age
    - Relapse includes medullary and/or extramedullary disease. CAR T cells have shown activity against extramedullary disease
- Prior to apheresis for T-cell collection, consider avoidance of agents that may significantly impact the absolute lymphocyte count and/or T-cell function
- The following lymphodepletion regimen is suggested prior to infusion of tisagenlecleucel (with alternatives allowed):
    - Fludarabine (30 mg/m^2 IV daily for 4 days)
    - Cyclophosphamide (500 mg/ m^2 IV daily for 2 days starting with first dose of fludarabine)
    - Infuse tisagenlecleucel 2 to 14 days after completion of lymphodepleting chemotherapy. Recommend evaluation of response 28 days after tisagenlecleucel infusion.
- Recommendations for toxicity management of cytokine release syndrome (CRS) or neurotoxicity are included in the tisagenlecleucel package insert. Tocilizumab and corticosteroids are the main options used to manage CRS and neurotoxicity. See the American Society for Transplantation and Cellular Therapy (ASTCT, formerly ASBMT) consensus grading and CARTOX management guidelines for detailed CAR T-cell toxicity grading, monitoring and management.

- Hypogammaglobulinemia: monitor IgG levels after treatment with tisagenlecleucel and replace with IV or subcutaneous immunoglobulin per standard guidelines (generally accepted to replete for IgG < 400 mg/dL).
- Patients may be monitored for B-cell aplasia (BCA) as a surrogate measure of functional CAR T-cell persistence.
- The role of consolidative allogeneic HSCT following tisagenlecleucel is unclear. Persistence of tisagenlecleucel (persistence of BCA) has been associated with durable clinical responses without subsequent HSCT.
- There is no consensus of the role of subsequent vaccination in patients with functional persistence of CAR T cells.
- Encourage patient participation in the center of International Blood and Marrow Transplant Research (CIBMT) Cellular Therapy Registry

Tisagenlecleucel is associated with CRS, including fatal or life-threatening reactions. Do not administer to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab. Neurologic toxicities, which may be serve or life-threatening, can occur following treatment, including concurrently with CRS. Monitor for neurologic events after treatment. Provide support care as needed. Tisagenlecleucel is available only through a restricted program under REMS.

The CIBMRT tracks safety and efficacy data following commercial CAR T-cell therapy.

CAR-T Cells
The generation of CAR-T cells to treat B-ALL is a significant advancement in the field. The treatment of patients with CAR-T cells has served as a bridge to transplant, enabling patients who were formerly unable to receive a transplant due to poor remission status to achieve a CR and ultimately transplantation. It is also reported that patients who received CAR-T cells can maintain long-term remission without subsequent HSCT.

NCCN Recommendations for Ph-Negative or Ph-Like ALL
Front-Line Management: The panel recommends that pediatric and AYA patients with Ph-negative or Ph-like ALL be treated in a clinical trial when possible. In the absence of an appropriate clinical trial, patients are initially grouped according to their risk criteria and induction therapy consists of multiagent chemotherapy. Patients who are MRD negative after induction will continue risk-stratified therapy. Patients who are MRD positive after induction may undergo intensified consolidation therapy. If MRD remains persistent other options include blinatumomab or tisagenlecleucel (category 2B recommendation). In all cases, HSCT may be considered part of consolidation or maintenance therapy.

R/R Management: For pediatric and AYA patients with Ph-negative or Ph-like ALL experiencing early or late first relapse, the panel recommends initial treatment with systemic therapy. If patients experience CR (CR2) and are MRD negative, the options are to receive blinatumomab (if in early first relapse) or continue on chemotherapy and receive maintenance therapy or HSCT if feasible based on the risk of subsequent relapse.

If patients experience CR2 and are MRD positive, or are experiencing first relapse after prior HSCT, in addition to chemotherapy, blinatumomab, tisagenlecleucel and inotuzumab ozogamicin may be considered prior to either a first or second HSCT. If patients experience less than a CR (i.e., multiple relapse), treatment options include chemotherapy, blinatumomab, tisagenlecleucel, or InO may be considered prior to either a first or second HSCT. If patients experience less then CR (i.e., multiple relapses), treatment options include chemotherapy, blinatumomab, tisagenlecleucel, or InO , and they may receive HSCT as consolidation therapy if their disease subsequently responds to therapy. Long-term remissions have been also reported after tisagenlecleucel treatment without subsequent HSCT. If the disease does not respond to therapy, alternative treatment options may be considered with best supporting and palliative care.

NCCN Recommendations for Ph-Positive ALL
Ph-positive ALL is relatively rare in pediatric patients, and the development of TKIs has improved previously poor treatment outcomes. The management of Ph-positive B-ALL is based on a number of clinical trials.

Front -Line Management: The panel recommends that pediatric and AYA patients with Ph-positive ALL be treated in a clinical trial that incorporates TKIs when possible. In the absence of an appropriate clinical trial, patients are treated with chemotherapy and a TKI. After a response assessment, standard risk patients (i.e., low MRD) continue consolidation chemotherapy and maintenance therapy with a TKI. As an alternative for maintenance, HSCT may be considered. In patients who are at high risk (i.e., less than CR, MRD+ at the end of consolidation), additional options include blinatumomab and tisagenlecleucel (category 2B recommendation). In these patients, consolidation with HSCT is recommended and post-transplant TKI should be considered. Of note, HSCT is not required but may be considered for Ph-positive ALL in CR-1.

R/R management: The NCCN Panel recommends for pediatric and AYA patients with R/R Ph-positive ALL are similar to what has been summarized for R/R Ph-negative or Ph-like ALL. If feasible, BCR-ABL1 kinase domain mutation analysis (e.g., T315I) should be performed and appropriate TKI should be added to the regimen.

B-Cell Lymphomas Version 5.2022

Guidance for Treatment of Patients with Chimeric Antigen Receptor (CAR) T-Cell Therapy

Tisagenlecleucel
Patient Selection

- Tisagenlecleucel is indicated in the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL and high- grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

- Health care facilities that dispense and administer Tisagenlecleucel must be enrolled and comply with Risk Evaluation and Mitigation Strategies (REMS) requirements.
- CRS management - See CART- Cell Related Toxicities
- Neurologic toxicity management – See CAR T- Cell Related Toxicities
- Prolonged cytopenias
    - Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and tisagenlecleucel infusion.
- Hypogammaglobulinemia
    - B-cell aplasia and hypogammaglobulinemia can occur in patients with complete remission after tisagenlecleucel infusion.

Guidance for the Treatment of Patients with CAR T-Cell Therapy
Axicabtagene ciloclecleucel and tisagenlecleucel should only be dispensed and administered in health care facilities that are enrolled in and comply with Risk Evaluation and Mitigation Strategies (REMS) requirements.

CAR T-Cell Therapy
Axicabtagene ciloleucel or tisagenlecleucel are anti-CD19 CAR-T cell therapies that are FDA approved for the treatment of adult patients with relapsed/refractory DLBCL, HBBL and transformed follicular lymphoma (TFL) after $\geq$ 2 prior chemoimmunotherapy regimens based on the results for ZUMA-1 and JULIET trials. Axicabtagene ciloleucel is also approved for relapsed for refractory PMBL after $\geq$ 2 prior chemoimmunotherapy regimens.

Third Line and Subsequent Therapy
- Anti-CD-19 CAR-T Cell therapy (only after $\geq$ 2 lines of systemic therapy)
    - Axicabtagene clioleucel

Histologic Transformation to DLBCL
- Anti-CD-19 CAR T-Cell Therapy (only after $\geq$ 2 lines of chemoimmunotherapy regimens)
    - Axicabtagene clioleucel
    - Lisocabtagene maraleucel
    - Tisagenlecleucel

Histologic Transformation of Nodal MZL to DLBCL
- Anti-CD-19 CAR T-Cell Therapy (only after $\geq$ 2 lines of chemoimmunotherapy regimens)
    - Axicabtagene clioleucel
    - Liscabtagene maraleucel
    - Tisagenlecleucel

Histologic Transformation after Minimal or No Prior Therapy
Based on the FDA approval, chimeric antigen receptor (CAR) T-cell therapy (axicabtagene ciloleucel or tisagenlecleucel) is included as an option for patients who have received ≥ 2 prior chemoimmunotherapy regimens for indolent or transformed disease.

For patients receiving PR to initial therapy of TFL, treatment options include second line regimens for DLBCL, allogeneic HCT with or without ISRT (only in the context of a clinical trial), CAR T-cell therapy (axicabtagene ciloleucel or tisagenlecleucel for patients who have received ≥ 2 prior chemoimmunotherapy regimens for indolent or transformed disease) if not previously given, or ISRT for localized residual disease and/or residual FDG – avid disease not previously irradiated. However, it should be noted that data on the insufficiency of transplant in patients who have received CAR T-cell therapy are not available. HDT/ASCR is not recommended after CAR-T cell therapy. Allogeneic HCT could be considered but remains investigational.

High Grade B-Cell Lymphomas with Translocation of MYC and BCL2 and/or BCL6
Relapsed/refractory disease should be managed as described for DLBCL. However, limited data are available regarding the outcome of relapsed/refractory disease following HDT/ASCR or allogeneic HCT in patients with HGBL with translocation of MYC and BCL2 and/or BCL6 or DEL. Polatzumab vedotin + BR is an appropriate treatment option for patients with relapsed or refractory HGBL with translocations of MYC and BCL2 and/or BCL6 (after ≥ 2 prior lines of therapies) ineligible for HDT/ASCR. CAR T-cell therapy (axicabtagene ciloleucel or tisagenlecleucel) is FDA approved for the treatment of relapsed/refractory HGBL after ≥ 2 prior systemic therapy regimens.

National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
The National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium (accessed October 2022) include the following category 2A recommendations for Kymriah (tisagenlecleucel).

Acute Lymphoblastic Leukemia - Acute Lymphoblastic Leukemia
Single-agent therapy for:

- Relapsed/refractory Philadelphia chromosome-positive B-ALL in patients <26 years and with refractory disease or ≥ 2 relapses and failure of 2 TKIs
- Relapsed/refractory Philadelphia chromosome-negative B-ALL in patients <26 years and with refractory disease or ≥ 2 relapses (preferred)

FDA Indication

Pediatric and Young Adult Relapsed or Refractory (r/r) B-cell Acute Lymphoblastic Leukemia (ALL): Tisagenlecleucel is indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse.

Adult Relapsed or Refractory (r/r) Diffuse Large B-Cell Lymphoma (DLBCL): Tisagenlecleucel is indicated for the treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

Limitation of Use: Tisagenlecleucel is not indicated for treatment of patients with primary central nervous system lymphoma.

Pediatric Acute Lymphoblastic Leukemia - Pediatric Acute Lymphoblastic Leukemia
Single-agent therapy for:

- Ph-negative or Ph-like B-ALL that is minimal residual disease positive (MRD+) after consolidation therapy
- Ph-positive B-ALL with less than complete response or MRD+ at end of consolidation
- relapsed/refractory Ph-negative B-ALL that is refractory or ≥2 relapses
- relapsed/refractory Ph-positive TKI intolerant/refractory B-ALL or relapse post-HSCT

FDA Indication

Pediatric and Young Adult Relapsed or Refractory (r/r) B-cell Acute Lymphoblastic Leukemia (ALL): Tisagenlecleucel is indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse.

Adult Relapsed or Refractory (r/r) Diffuse Large B-Cell Lymphoma (DLBCL): Tisagenlecleucel is indicated for the treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

Limitation of Use: Tisagenlecleucel is not indicated for treatment of patients with primary central nervous.

B-Cell Lymphomas - Post-Transplant Lymphoproliferative Disorders
Treatment for monomorphic PTLD (B-cell type) as

- Additional therapy for patients with intention to proceed to transplant who have partial response following second line chemoimmunotherapy for relapsed or refractory disease
- Treatment of disease in second relapse or greater (if anti-CD19 CAR T-cell therapy not previously given)

FDA Indication

P**ediatric and Young Adult Relapsed or Refractory (r/r) B-cell Acute Lymphoblastic Leukemia (ALL):** Tisagenlecleucel is indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse.

Adult Relapsed or Refractory (r/r) Diffuse Large B-Cell Lymphoma (DLBCL): Tisagenlecleucel is indicated for the treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

Limitation of Use: Tisagenlecleucel is not indicated for treatment of patients with primary central nervous system lymphoma.

B-Cell Lymphomas - Histologic Transformation of Nodal Marginal Zone Lymphoma to Diffuse Large B-Cell Lymphoma
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)

FDA Indication

Pediatric and Young Adult Relapsed or Refractory (r/r) B-cell Acute Lymphoblastic Leukemia (ALL): Tisagenlecleucel is indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse.

Adult Relapsed or Refractory (r/r) Diffuse Large B-Cell Lymphoma (DLBCL): Tisagenlecleucel is indicated for the treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

Limitation of Use: Tisagenlecleucel is not indicated for treatment of patients with primary central nervous.

B-Cell Lymphomas - Follicular Lymphoma (grade 1-2)
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
- 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)

FDA Indication

Pediatric and Young Adult Relapsed or Refractory (r/r) B-cell Acute Lymphoblastic Leukemia (ALL): Tisagenlecleucel is indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse.

Adult Relapsed or Refractory (r/r) Diffuse Large B-Cell Lymphoma (DLBCL): Tisagenlecleucel is indicated for the treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

Limitation of Use: Tisagenlecleucel is not indicated for treatment of patients with primary central nervous system lymphoma.

B-Cell Lymphomas - Diffuse Large B-Cell Lymphoma
Used for 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
- 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

FDA Indication

P**ediatric and Young Adult Relapsed or Refractory (r/r) B-cell Acute Lymphoblastic Leukemia (ALL):** Tisagenlecleucel is indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse.

Adult Relapsed or Refractory (r/r) Diffuse Large B-Cell Lymphoma (DLBCL): Tisagenlecleucel is indicated for the treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

Limitation of Use: Tisagenlecleucel is not indicated for treatment of patients with primary central nervous system lymphoma.

B-Cell Lymphomas - AIDS-Related B-Cell Lymphomas
Used for relapsed AIDS-related diffuse large B-cell lymphoma, primary effusion lymphoma, and HHV8-positive diffuse large B-cell lymphoma, not otherwise specific (NOS) as

- Additional therapy for patients with intention to proceed to transplant who have partial response following second-line therapy for relapsed or refractory disease
- Treatment (if anti-CD19 CAR T-cell therapy 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

FDA Indication

Pediatric and Young Adult Relapsed or Refractory (r/r) B-cell Acute Lymphoblastic Leukemia (ALL): Tisagenlecleucel is indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse.

Adult Relapsed or Refractory (r/r) Diffuse Large B-Cell Lymphoma (DLBCL): Tisagenlecleucel is indicated for the treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

Limitation of Use: Tisagenlecleucel is not indicated for treatment of patients with primary central nervous system lymphoma.

B-Cell Lymphomas - 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
- 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

FDA Indication

Pediatric and Young Adult Relapsed or Refractory (r/r) B-cell Acute Lymphoblastic Leukemia (ALL): Tisagenlecleucel is indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse.

Adult Relapsed or Refractory (r/r) Diffuse Large B-Cell Lymphoma (DLBCL): Tisagenlecleucel is indicated for the treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

Limitation of Use: Tisagenlecleucel is not indicated for treatment of patients with primary central nervous system lymphoma.

REGULATORY STATUS
On August 30, 2017, tisagenlecleucel (Kymriah™; Novartis) was approved by the Food and Drug Administration (FDA) for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. Kymriah™ is not indicated for the treatment of patients with primary central nervous system lymphoma.

On May 1, 2018, tisagenlecleucel (Kymriah™; Novartis) was approved by the Food and Drug Administration (FDA) for the treatment of adult patients with relapsed or refractory large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DCBCL), high grade B-cell lymphoma and DLBCL arising from follicular lymphoma. Kymriah™ is not indicated for the treatment of patients with primary central nervous system lymphoma.

PRIOR APPROVAL

Prior approval required.

POLICY

See related medical policies:

- 08.01.27 Cellular Immunotherapy for Prostate Cancer – Provenge (Sipuleucel-T)
- 08.01.29 Yescarta (Axicabtagene Ciloleucel)*
- 08.01.33 Tecartus (Brexucabtagene Autoluecel)*
- 08.01.34 Breyanzi (Lisocabtagene Maraluecel)*
- 08.01.5 Abecma (Idecabtagene Vicleucel)*
- 08.01.36 Carvykti (Ciltacabtagene Autoleucel)*

Pediatric and Young Adult Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia (ALL)

Kymriah (Tisagenlecleucel) as a one-time, single administration intravenous infusion is considered medically necessary when ALL the following criteria are met:

- Confirmed diagnosis of CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL) with morphologic bone marrow tumor involvement (≥5% lymphoblasts): **AND**
- One of the following:
    - Disease is refractory or in second or later relapse; **or**
    - Minimal residual disease (MRD) positive after consolidations therapy; **or**
    - Philadelphia chromosome-positive disease (Ph + B-ALL) **and** one of the following:
        - Less than complete response (CR)
        - High risk genetics*
        - Tried and failed or is intolerant (e.g., toxicity [adverse event(s)]) to at least 2 tyrosine kinase inhibitors (TKIs) (e.g., imatinib (gleevac), dasatinib (sprycel), nilotinib (tasigna), ponatinib (iclusig), bosutinib (bolsulif)
        - Relapse post-hematopoietic stem cell transplantation; **AND**
- Are 25 years old or younger at the time of infusion; **AND**
- Have not received prior treatment with Kymriah (tisagenlecleucel) or any other gene therapy including other CAR-T therapies; or are being considered for treatment with any other gene therapy; **AND**
- Have adequate organ function
    - Creatinine clearance $\geq$ 60 mL/min
    - A serum creatinine of $\leq$ 1.5 times upper limit of normal
    - ALT (alanine aminotransferase) $\leq$ 5 times upper limit of normal for age
    - Bilirubin $\leq$ 2.0 mg/dl except for patients with Gilbert-Meulengracht syndrome; patients with Gilbert-Meulengracht syndrome may be included if their total bilirubin is $\leq$ 3.0 times the upper limit of normal
    - Direct bilirubin $\leq$ 1.5 times upper limit of normal
    - Hemodynamically stable and left ventricular ejection fraction (LVEF) $\geq$ 45% confirmed by echocardiogram or multigated acquisition (MUGA) scan; **AND**
- Kymriah (tisagenlecleucel) will be provided based on the FDA recommended dosing and administration:
    - If the patient is 50 kg or less in weight, they will receive weight-based dosing at 0.2 to 5.0 x 10^6 CAR-positive viable T-cells per kg of body weight intravenously; **or**
    - If the patient is above 50 kg in weight, the patient will not be treated with more than 2.5 x 10^8 total CAR-positive T cells intravenously; **AND**
- The patient will be receiving Kymriah (tisagenlecleucel) at a treatment center that is certified to administer Kymriah (tisagenlecleucel); **AND**
- Do not have any of the following:
    - Burkitt lymphoma.

- Active hepatitis B (HBsAG positive) or hepatitis C (anti-HCV positive), if viral load is detectable; a history of hepatitis B or hepatitis C is permitted if the viral load is undetectable per quantitative PCR and/or nucleic acid testing.
- Presence of fungal, bacterial, viral or other infection that is uncontrolled requiring IV antimicrobials (antibiotics, antifungals, antiprotozoals, antivirals) for management prior to Kymriah (tisagenlecleucel) infusion.
- Active graft versus host disease (GVHD).
- Donor lymphocyte infusion within 6 weeks prior to Kymriah (tisagenlecleucel) infusion.
- Active central nervous system (CNS) involvement, NCCN guidelines define CNS involvement (CNS leukemia CNS-3) as the following: a white blood cell (WBC) count of $\geq$5 leukocytes/mcL in the cerebrospinal fluid (CSF) with the presence of lymphoblasts):

  Note:

  - Patient with central nervous system 2 disease [cerebrospinal fluid containing blasts, but <5 white blood cells per microliter] are eligible.
  - If the patient has leukemic cells in the peripheral blood and the lumbar puncture (LP) is traumatic and WBC $\geq$5/mcL in the CSF with blasts, then compare the CSF WBC/red blood cell (RBC) ratio to the blood WBC/RBC ratio. If the CSF ratio is at least two-fold greater than the blood ratio, then the classification is CNS-3; if not then it is CNS-2.

Kymriah (tisagenlecleucel) is considered **investigational** for all other indications as the safety and efficacy has not yet been established in the peer reviewed medical literature. The evidence is insufficient to determine the effects on net health outcomes.

Repeat Treatment
Repeat treatment of Kymriah (tisagenlecleucel) is considered **investigational**, the safety and efficacy beyond one dose has not been studied and is also not indicated in the current FDA approval for Kymriah (tisagenlecleucel). The evidence is insufficient to determine the effects on net health outcomes.

Definitions:
Relapsed disease describes the reappearance of leukemia cells in the bone marrow or peripheral blood after the attainment of a complete remission with chemotherapy and/or 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).

***Pediatric Genetic Risk Groups for B-ALL**

Risk Group	Genetics

Unfavorable Risk Features	• Hypodiploidy (<44 chromosomes)
	• KMT2Ar (t[4;11] or others)
	• t(9:22)(q34;q11):BCR-ABL1
	• BCR-ABL1-like (Ph-like) ALL
	  ▪ JAK-STAT (CRLF2r,EPORr, JAK1/2/3/, TYK2r, mutations of SH2B3, ILTR, JAK1/2/3
	  ▪ ABL class (rearrangements of ABL1, ABL2, PDGFRA, PDGFRB, FGFR0
	  ▪ Other (NTRKr, FLT3r, LYnr, PTK2Br)
	• t(17;19): TCF3-HLF fusion
	• Intrachromosomal amplification of chromosome 21 (iAMP2f)
	• Alterations of IKZF1

***Adult and AYA Cytogenetic Risk Groups for B-ALL**

Risk Group	Cytogenetics
Poor Risk	• Hypodiploidy (<44 chromosomes) • KMT2Ar (t[4;11] or others) • t(v,14q32)/IgH • t(9;22)(q34,q11.20: BCR0ABL-1 (defined as high risk in the pre-TKI era) • Complex karyotype (5 or more chromosomal abnormalities) • Ph-like ALL; intrachromosomal amplification of chromosome 21 (iAMP21)

Relapsed or Refractory Large B-cell Lymphoma
Kymriah (tisagenlecleucel) as a one-time, single administration intravenous infusion is considered medically necessary when ALL the following criteria are met:

- Adult patients 18 years and older; **AND**
- The individual has a histologically confirmed diagnosis of one of the following subtypes of relapsed or refractory large B-cell lymphoma:
    - Diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS); **or**
    - AIDS related diffuse large B-cell lymphoma (DLBCL); **or**
    - Primary effusion lymphoma; **or**
    - HHV8 positive diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS); or
    - High grade B-cell lymphoma not otherwise specified (NOS0; **or**
    - High grade B-cell lymphoma with translocations of MYC and BCL2 and/or BCL6 (double/triple hit lymphoma); **or**
    - Monomorphic post-transplant lymphoproliferative disorders, B-cell type; **or**
    - Histologic transformation of nodal marginal zone lymphoma to diffuse large B-cell lymphoma (DLBCL); **or**
    - Histologic transformation of follicular lymphoma (grade 1-2) to diffuse large B-cell lymphoma (DLBCL); **AND**
- Patients must have received prior therapy including at a minimum:
    - Two or more lines of systemic chemotherapy and disease is refractory or relapsed; **or**
    - For an individual with histologic transformation of follicular lymphoma or histologic transformation of nodal marginal zone lymphoma to diffuse large B-cell lymphoma (DLBCL) must have received $\geq$2 prior chemotherapy regimens which included at least one anthracycline (e.g., doxorubicin) or anthracenedione unless contraindicated and subsequently have chemo-refractory disease after transformation to diffuse large B-cell lymphoma (DLBCL); **AND**
- Renal function defined as:
    - A serum creatinine of $\leq$ 1.5 times upper limit of normal (ULN); **or**
    - Estimated glomerular filtration rate (eGFR) $\geq$ 60 mL/min/1.73 m^2; **AND**
- Liver function defined as:
    - ALT (alanine aminotransferase) $\leq$ 5 times upper limit of normal for age; **and**
    - Bilirubin $\leq$ 2.0 mg/dl except for patients with Gilbert-Meulengracht syndrome; patients with Gilbert-Meulengracht syndrome may be included if their total bilirubin is $\leq$ 3.0 times the upper limit of normal; **and**
    - Direct bilirubin $\leq$ 1.5 times upper limit of normal; **AND**
- Baseline oxygen saturation > 91% on room air; **AND**
- Hemodynamically stable and left ventricle ejection fraction (LVEF) $\geq$ 45% confirmed by echocardiogram or multigated acquisition (MUGA) scan; **AND**
- Adequate bone marrow reserve defined as:

    - Absolute neutrophil count (ANC) > 1000/uL; **and**
    - Absolute lymphocyte count (ALC) ≥ 300/uL; **and**
    - Platelets ≥ 50,000/uL; **and**
    - Hemoglobin > 8.0 g/dl; **AND**
- Kymriah (tisagenlecleucel) will be provided based on the FDA recommended dosing and administration:
    - For patients 18 years of age through age 24 years of age:
        - If the patient is 50 kg or less in weight, they will receive weight-based dosing at 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg body weight intravenously; **or**
        - If the patient is above 50 kg in weight, the patient will not be treated with more than 2.5 x 10^8 total CAR-positive viable T cells intravenously.
    - For patients 25 years and older:
        - The patient will not be treated with more than 6.0 x 10^8 CAR-positive viable T cells intravenously; **AND**
- The patient will be receiving Kymriah (tisagenlecleucel) at a treatment center that is certified to administer Kymriah (tisagenlecleucel); **AND**
- Do not have any of the following:
    - Prior treatment with CAR-T therapies or any other gene therapy; or are being considered for treatment with any other gene therapy.
    - Active central nervous system (CNS) lymphoma by imaging.
    - Presence of fungal, bacterial, viral, or other infection that is uncontrolled requiring IV antimicrobials (antibiotics, antifungals, antiprotozoals, antivirals) for management prior to Kymriah (tisagenlecleucel) infusion)
    - Active hepatitis B (HBsAG positive) or hepatitis C (anti-HCV positive), if viral load is detectable; a history of hepatitis B or hepatitis C is permitted if the viral load is undetectable per quantitative PCR and/or nucleic acid testing).

Kymriah (tisagenlecleucel) is considered **investigational** for all other indications as the safety and efficacy has not yet been established in the peer reviewed medical literature. The evidence is insufficient to determine the effects on net health outcomes.

Repeat Treatment
Repeat treatment of Kymriah (tisagenlecleucel) for any indication is considered **investigational**, the safety and efficacy beyond one dose has not been studied and is also not indicated in the current FDA approval for Kymriah (tisagenlecleucel). The evidence is insufficient to determine the effects on net health outcomes.

Definitions:
Relapsed Disease reflects the appearance of any new lesion after attainment of an initial complete remission. When relapse is suspected a biopsy of the involved lymph node or mass is recommended to confirm relapse and evaluate for potential change in histology.

Refractory Disease or resistant DCBCL is suggested by less than 50 percent decrease in lesion size with treatment in the absence of new lesion development.

Policy Guidelines
Required Documentation: The patient's medical records submitted for review should document the above medical necessity criteria is met for the indication being requested and should also include the following:

- Office notes that contain the confirmed diagnosis and clinical features of the diagnosis (including any laboratory results confirming the diagnosis e.g., for patients with B-cell ALL laboratory results for CD19 tumor expression), relevant history and physical and prior cancer treatment history.
- Include patient's weight for dosing and administration review.
- Lab work within 7 to 14 days of the approval request to determine the individual has adequate organ and bone marrow function and meets the medical necessity criteria above.

Harvesting
Autologous lymphocytes used as part of adoptive immunotherapy may be harvested in a pheresis (leukapheresis) procedure or may be isolated from resected tumor tissue.

Central Nervous System (CNS) Disease for B-Cell Acute Lymphoblastic Leukemia
Central nervous system (CNS) disease for B-cell acute lymphoblastic leukemia is defined by the following groups:

- **CNS 1**: No lymphoblasts in the cerebrospinal fluid (CSF), regardless of the white blood cell (WBC) count
- **CNS 2**: A white blood cell (WBC) count of less than 5 leukocytes/mcL in the cerebral spinal fluid (CSF) with the presence of blasts
- **CNS 3**: A white blood cell (WBC) count of 5 leukocytes/mcL or greater with the presence of blasts

Note: If the patient has leukemic cells in the peripheral blood and the lumbar puncture (LP) is traumatic and WBC $\geq$5/mcL in the CSF with blasts, then compare the CSF WBC/red blood cell (RBC) ratio to the blood WBC/RBC ratio. If the CSF ratio is at least two-fold greater than the blood ratio, then the classification is CNS-3; if not then it is CNS-2

Black Box Warning
Kymriah™ (tisagenlecleucel) has a black box warning because of the risk of cytokine release syndrome and neurologic toxicities that include fatal or life-threatening reactions. It should not be administered to patients with active infection or inflammatory disorders. It is recommended that severe or life-threatening cytokine release syndrome should be treated with tocilizumab. Patients should be monitored for neurologic events after treatment.

Kymriah™ (tisagenlecleucel) is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). The requirement for the REMS components are as follows:

- Health care facilities that dispense and administer Kymriah (tisagenlecleucel) must be enrolled and comply with the REMS requirements.
- Certified health care facilities must have onsite, 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 Kymriah (tisagenlecleucel), if needed for treatment of cytokine release syndrome (CRS).
- Certified health care facilities must ensure that health care providers who prescribe, dispense or administer Kymriah (tisagenlecleucel) are trained about the management of cytokine release syndrome (CRS) and neurologic toxicities.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- Q2042 Tisagenlecleucel, up to 600 million car-positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose (Kymriah)
- 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., cyroperservation, 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
- Revenue Code 0891 – Special Process Drugs – FDA Approved Cell Therapy

SELECTED REFERENCES

- Berry DA, Zhou S, Higley H, et al. Association of minimal residual disease with clinical outcome in pediatric and adult acute lymphoblastic leukemia: a meta-analysis. *JAMA Oncol.* Jul 13 2017;3(7):e170580. PMID 28494052
- Hunger SP, Mullighan CG. Acute lymphoblastic leukemia in children. *N Engl J Med.* Oct 15 2015;373(16):1541-1552. PMID 26465987
- Maude SL, Teachey DT, Porter DL, et al. CD19-targeted chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. *Blood.* Jun 25 2015;125(26):4017-4023. PMID 25999455
- Pui CH, Carroll WL, Meshinchi S, et al. Biology, risk stratification, and therapy of pediatric acute leukemias: an update. *J Clin Oncol.* Feb 10 2011;29(5):551-565. PMID 21220611

- Tallen G, Ratei R, Mann G, et al. Long-term outcome in children with relapsed acute lymphoblastic leukemia after time-point and site-of-relapse stratification and intensified short-course multidrug chemotherapy: results of trial ALL-REZ BFM 90. *J Clin Oncol.* May 10 2010;28(14):2339-2347. PMID 20385996
- Bajwa R, Schechter T, Soni S, et al. Outcome of children who experience disease relapse following allogeneic hematopoietic SCT for hematologic malignancies. *Bone Marrow Transplant.* May 2013;48(5):661-665. PMID 23128573
- Jeha S, Gaynon PS, Razzouk BI, et al. Phase II study of clofarabine in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. *J Clin Oncol.* Apr 20 2006;24(12):1917-1923. PMID 16622268
- von Stackelberg A, Locatelli F, Zugmaier G, et al. Phase I/phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. *J Clin Oncol.* Dec 20 2016;34(36):4381-4389. PMID 27998223
- UpToDate. Overview of the Treatment of Acute Lymphoblastic Leukemia in Children and Adolescents. Terzah M. Horton M.D., PhD, C. Philip Steuber M.D. Topic last updated March 1, 2019. Also available at e
- UpToDate. Treatment of Relapsed or Refractory Acute Lymphoblastic Leukmia in Adults. Richard A. Larson M.D.. Topic last updated April 12, 2019. Also available at https://www.uptodate.com
- UpToDate. Treatment of Relapsed or Refractory Diffuse Large B Cell Lymphoma. Arnold S. Freedman M.D., Jonathan W. Friedberg M.D., Topic last updated October 8, 2019. Also available at https://www.uptodate.com
- UpToDate. Histologic Transformation of Follicular Lymphoma. Arnold S. Freedman M.D., Jonathan W. Friedberg M.D., Topic last updated October 2, 2019. Also available at https://www.uptodate.com
- Immunotherapy for the Preventative and Treatment of Relapse Following Allogeneic Hematopoietic Cell Transplantation. Robert S. Negrin M.D., Topic last updated November 1, 2018. Also available at https://www.uptodate.com
- Kymriah. Also available at https://www.us.kymriah.com/acute-lymphoblastic-leukemia
- Kymriah Package Insert – FDA. Also available at https://www.fda.gov/downloads/BiologicsBloodVaccines.com
- FDA News Release. FDA Approval Brings First Gene Therapy to the United States. Kymriah (tisagenlecleucel) for certain pediatric and young adult patients with a form or acute lymphoblastic leukemia (ALL). Also available at https://www.fda.gov
- FDA News Release – FDA approves CAR-T cell therapy to treat adults with certain tuypes of large B-cell lymphoma. Also availabe at https://www.fda.gov/NewEvents/Newsroom/PressAnnouncements/ucm581216.htm
- Novartis Press Release: Kymriah (Tisagenlecleucel) receives second FDA approvals to treat appropriate relapsed or refractory patients with large B-cell lymphoma. Also available at https://www.novartis.com

- Kymriah package insert – FDA revised May 2018. Also available at https://www.fda.gov
- U.S. Food and Drug Administration FDA Supplement Approval May 1, 2018 for Kymriah for relapsed or refractory large B-cell lymphoma. Also available at https://www.fda.gov
- U.S. FDA Advisory Committee Briefing Document Tisagenlecleucel (CTL019) for the treatment of pediatric and young adult patietns with relapsed/refractory B-cell acute lymphoblastic leukemia. July 12, 2017
- National Comprehensive Cancer Network (NCCN) Acute Lymphoblastic Leukemia Version 1.2022. Also available at https://www.nccn.org
- National Comprehensive Cancer Network (NCCN) Pediatric Acute Lymphoblastic Leukemia 1.2022. Also available at https://www.nccn.org
- National Comprehensive Cancer Network (NCCN) B-Cell Lymphomas Version 5.2022. Also available at https://www.nccn.org
- National Comprehensive Cancer Network (NCCN) Drugs and Biologics Accessed October 2022. Also available at https://www.nccn.org
- ECRI. Panel Providers Guidelines for Managing CAR-T Cell Toxicities. Published November 30, 2017. Also available at https://www.ecri.org
- ECRI. FDA Expands Kymriah Immunotherapy Approval for Large B-Cell Lymphoma. Published May 8, 2018. Also available at https://www.ecri.org
- ECRI. Kymriah (Tisagenlecleucel) (Novartis Pharmaceuticals Corp.) for Treatment Diffuse Large B-Cell Lymphoma. Published June 25, 2018. Also available at https://www.ecri.org
- Friedberg JW. Relapsed/Refractory Diffuse Large B-Cell Lymphoma. Hematology Am Soc Hematol Educ Program. 2011:2011:498-505
- Crump M, Neelapu SS, Farooq U. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood 2017 Oct 19:130(16):1800-1808.
- Porter D, Hwang WT, Frey NV, et. al. Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia Sci. Transl Med 2015 Sep 2:7(303):303ra139. PMID 26333935
- JULIET phase II clinical trial (NCT02445248)
- Key Statistics for Non=Hodgkin Lymphoma. Also available at https://www.cancer.org
- Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. Jan 03 2019; 380(1): 45-56. PMID 30501490
- Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med. Feb 01 2018; 378(5): 439-448. PMID 29385370
- Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. Apr 2019; 25(4): 625-638. PMID 30592986

- Hayes Inc. Tisagenlecleucel (Kymriah) for Treatment of Relapsed or Refractory CD19+ B-Cell Malignancies. Prevision Therapy Assessment. Annual Review August 31, 2021

POLICY HISTORY

Date	Reason	Action
October 2022	Annual Review	Policy Renewed
October 2021	Annual Review	Policy Revised
October 2020	Annual Review	Policy Revised
November 2018	Interim Review	Policy Revised
October 2018	Content moved from Medical Policy 08.01.26	New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

*CPT® is a registered trademark of the American Medical Association.