DRAFT

BlueCross BlueShield of Alabama

"Unless otherwise noted, coverage for specific indications is effective the date of the FDA approval of that indication."
"Please check Approved by Governing Bodies for FDA approval date."

Name of Blue Advantage Policy:
Kymriah™ (tisagenlecleucel)

Policy #: 675
Category: Pharmacy

Effective Date: July 1, 2018
Last Review Date: January 2018

Background:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Description of Procedure or Service:

Kymriah is a CD-19 directed genetically modified autologous T cell immunotherapy which involves the reprogramming of T cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD-19-expressing malignant and normal cell. CD-19 is an antigen expressed on the surface of B-cells and tumors derived from B-cells. Upon binding to CD-19 expressing cells, the CAR transmits a signal to promote T-cell expansion, activation, target cell elimination, and persistence of the Kymriah cells.

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.

Policy:

Effective for dates of service on and after July 1, 2018:

Blue Advantage will treat **Kymriah™ (tisagenlecleucel)** as a **covered benefit** for the treatment of **B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse** when **all** of the following criteria are met:

- Confirmed diagnosis of CD-19-positive B-cell acute lymphoblastic leukemia with morphologic bone marrow tumor involvement (≥ 5% lymphoblasts); **and**
- Disease is refractory or in second or later relapse defined as **ONE** of the following:
  - Second or greater bone marrow (BM) relapse; **or**
  - Any BM relapse after allogeneic stem cell transplantation (SCT); **or**
  - Primary refractory (not achieving a complete response after 2 cycles of standard chemotherapy or chemorefractory (not achieving a complete response after 1 cycle of standard chemotherapy for relapsed disease); **or**
  - Patients with Philadelphia chromosome (Ph)-positive disease have a contraindication, intolerance, or have failed two prior lines of tyrosine kinase inhibitor (TKI) therapy (e.g., imatinib, dasatinib, ponatinib, etc.); **or**
  - Patient is not eligible for allogeneic SCT
- Are 25 years of age or younger at the time of infusion; **and**
- Have not received prior treatment with tisagenlecleucel or any other gene therapy or are being considered for treatment with any other gene therapy; **and**
- Kymriah™ can be administered during inpatient hospitalization only; **and**
- Kymriah™ will be given as a one-time, single administration treatment; **and**
- Have not received radiation therapy or systemic therapy within 2 weeks of leukapheresis or planned CAR-T infusion; **and**
- Have adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis, as evidence by, including but not limited to the following:
  - Serum creatinine ≤ 1.5 mg/dL
  - ALT/AST < 5 times the upper limit of normal

- Total bilirubin < 2.0mg/dL
- Cardiac ejection fraction ≥ 45% confirmed by echocardiogram
- No evidence of pericardial effusion as evident by echocardiogram

- Do not have any of the following:
  - Burkitt's lymphoma
  - Any central nervous system (CNS) disease (i.e., history or presence of CNS disorders such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or autoimmune disease with CNS involvement)
  - History of or active HIV, hepatitis B, or hepatitis C
  - Any uncontrolled infection requiring IV antimicrobials for management
  - Active inflammatory disorder (ongoing use of systemic corticosteroids or other immunosuppressive treatment)
  - Active autoimmune disease requiring systemic treatment in the previous 2 years (excluding replacement therapy)
  - History of malignancy except carcinoma in situ of the skin or cervix with curative intent and no evidence of active disease
  - History of other invasive malignancy (unless the patient is currently disease-fee and in complete remission for > 5 years
  - Grade 2 to 4 graft-versus-host disease
  - Concomitant genetic syndrome with the exception of Down's syndrome
  - Received allogeneic cellular therapy, such as donor lymphocyte infusion within 6 weeks prior to tisagenlecleucel infusion
  - Active central nervous system 3 (CNS3) malignancy involvement (i.e. white blood cell count ≥ 5cells/μL in cerebrospinal fluid with presence of lymphoblasts)
  - Investigational medicinal product or medical device product within the last 30 days prior to screening.

Blue Advantage will treat **Kymriah™ (tisagenlecleucel)** as a **covered benefit** for the treatment of **relapsed or refractory non-Hodgkin's lymphoma (NHL)** when documentation is provided to support **all** of the following criteria:

- 18 years of age or older at the time of infusion; **and**
- Histologically confirmed diagnosis of **one** of the following types of aggressive NHL:
  - Diffuse large B-cell lymphoma (DLBCL); **or**
  - Primary mediastinal large B-cell lymphoma; **or**
  - High-grade B-cell lymphoma; **or**
  - Diffuse large B-cell lymphoma arising from follicular lymphoma; **or**
- Relapsed or refractory disease, as defined below:
  - Relapsed disease defined as progression after two or more lines of systemic therapy (which may or may not include therapy supported by autologous stem cell transplant); **or**
  - Refractory disease defined as not having achieved an initial complete remission after 2 cycles of standard chemotherapy regiment or in second or greater relapse; **and**

- Received adequate prior therapy including, at a minimum, **all** of the following:
    - Anti-CD20 monoclonal antibody for CD20-positive tumor; **and**
    - An anthracycline containing chemotherapy regimen; **and**
- Have not received prior treatment with Kymriah or any other gene therapy or are being considered for treatment with any other gene therapy; **and**
- Have not received radiation therapy or systemic therapy within 2 weeks of leukapheresis or planned CAR-T infusion; **and**
- *ECOG performance status of 0-1; **and**
- Documentation of **all** of the following clinical findings within 2 weeks of planned leukapheresis:
    - Absolute neutrophil count (ANC) ≥1000/µL; **and**
    - Absolute lymphocyte count (ALC) >300/µL; **and**
    - Platelet count ≥75,000/µL; **and**
    - Hemoglobulin > 8.0g/dl; **and**
- Kymriah™ can be administered during inpatient hospitalization only; **and**
- Kymriah™ will be given as a one-time, single administration treatment; **and**
- Have adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis, as evidence by, including, but not limited to the following:
    - Serum creatinine ≤ 1.5mg/dL
    - ALT/AST ≤ 5 times the upper limit of normal
    - Total bilirubin ≤ 2 mg/dL
    - Cardiac ejection fraction ≥45% confirmed by echocardiogram
    - No evidence of pericardial effusion as evident by echocardiogram
    - No clinically significant pleural effusion
    - Minimum level of pulmonary reserve defined as < Grade 1 dyspnea and pulse oxygenation > 91% on room air
- Do not have any of the following:
    - CNS lymphoma
    - Any central nervous system (CNS) disease (i.e., history or presence of CNS disorders such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, autoimmune disease with CNS involvement)
    - History of or active HIV, hepatitis B, or hepatitis C
    - Any uncontrolled infection requiring IV antimicrobials for management
    - Active inflammatory disorder (ongoing use of systemic corticosteroids or other immunosuppressive treatment).
    - Active autoimmune disease requiring systemic treatment in the previous 2 years (excluding replacement therapy)
    - History of malignancy except carcinoma in situ (e.g. skin, cervix)
    - History of other invasive malignancy (unless the patient is currently disease-free and in complete remission for > 5 years)
    - Autologous stem cell transplant within 6 weeks prior to request for CAR-T
    - History of allogeneic stem cell transplantation
    - Unstable angina and/or myocardial infarction within 6 months prior to screening
    - Cardiac arrhythmia not controlled with medical management

- Taking oral anticoagulation medication
- Investigational medicinal product or medical device product within the last 30 days prior to screening
- Recent monoclonal antibody treatment including anti-CD20 therapy within 4 weeks prior to infusion or 5 half-lives of the respected antibody; whichever is longer.

Blue Advantage will treat **Kymriah™ (tisagenlecleucel)** as a **non-covered benefit** and as **investigational** when the above criteria are not met and for all other indications.

Additional Policy Guidelines

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

The recommended dosage of Kymriah™ for patients 50 kg or less is 0.2 to 5.0×10^6 chimeric antigen receptor positive viable T cells per kg body weight intravenously; for patients above 50 kg, dose is 0.1 to 2.5 x 10^8 total chimeric antigen receptor positive viable T cells (non-weight-based) intravenously.

Central nervous system (CNS) disease for B-cell acute lymphoblastic leukemia is defined by the following groups:

- **CNS 1**: Absence of blasts on cerebrospinal fluid cytospin preparation, regardless of the white blood cell (WBC) count
- **CNS 2**: WBC count of less than 5/mL and blasts on cytospin findings
- **CNS 3**: WBC count of 5/mL or more and blasts on cytospin findings and/or clinical signs of CNS leukemia (e.g., facial nerve palsy, brain/eye involvement, hypothalamic syndrome)

Kymriah™ is available only through a restricted program under a risk evaluation and mitigation strategy (REMS) called the Kymriah REMS. The requirement for the REMS components are as follows:

- Health care facilities that dispense and administer Kymriah™ 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™ infusion, if needed for treatment of cytokine release syndrome.
- Certified health care facilities must ensure that health care providers, who prescribe, dispense or administer Kymriah™, are trained about the management of cytokine release syndrome and neurologic toxicities.

Effective for dates of service on and after January 1, 2018 and prior to July 1, 2018:
Blue Advantage will treat **Kymriah™ (tisagenlecleucel)** as a **covered benefit** for the treatment of **B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse** when **all** of the following criteria are met:

- Confirmed diagnosis of CD-19-positive B-cell acute lymphoblastic leukemia with morphologic bone marrow tumor involvement (≥ 5% lymphoblasts); **and**
- Disease is refractory or in second or later relapse defined as **ONE** of the following:
  - Second or greater bone marrow (BM) relapse; **or**
  - Any BM relapse after allogeneic stem cell transplantation (SCT); **or**
  - Primary refractory (not achieving a complete response after 2 cycles of standard chemotherapy or chemorefractory (not achieving a complete response after 1 cycle of standard chemotherapy for relapsed disease); **or**
  - Patients with Philadelphia chromosome (Ph)-positive disease have a contraindication, intolerance, or have failed two prior lines of tyrosine kinase inhibitor (TKI) therapy (e.g., imatinib, dasatinib, ponatinib, etc.); **or**
  - Patient is not eligible for allogeneic SCT
- Are 25 years of age or younger at the time of infusion; **and**
- Have not received prior treatment with tisagenlecleucel or any other gene therapy or are being considered for treatment with any other gene therapy; **and**
- Kymriah™ can be administered during inpatient hospitalization only.
- Kymriah™ will be given as a one-time, single administration treatment; **and**
- Have not received radiation therapy or systemic therapy within 2 weeks of leukapheresis; **and**
- Have adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis, as evidence by, including but not limited to the following:
  - Serum creatinine ≤ 1.5 mg/dL
  - ALT/AST < 5 times the upper limit of normal
  - Total bilirubin < 2.0mg/dL
  - Cardiac ejection fraction ≥ 45%
  - No evidence of pericardial effusion as evident by echocardiogram
- Do not have any of the following:
  - Burkitt's lymphoma
  - Any central nervous system (CNS) disease (i.e., history or presence of CNS disorders such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or autoimmune disease with CNS involvement)
  - History of or active HIV, hepatitis B, or hepatitis C
  - Any uncontrolled infection requiring IV antimicrobials for management
  - Active inflammatory disorder (ongoing use of systemic corticosteroids or other immunosuppressive treatment)
  - Active autoimmune disease requiring systemic treatment in the previous 2 years (excluding replacement therapy)
  - History of malignancy except carcinoma in situ of the skin or cervix with curative intent and no evidence of active disease

- Grade 2 to 4 graft-versus-host disease
- Concomitant genetic syndrome with the exception of Down's syndrome
- Received allogeneic cellular therapy, such as donor lymphocyte infusion within 6 weeks prior to tisagenlecleucel infusion
- Active central nervous system 3 (CNS3) malignancy involvement (i.e. white blood cell count ≥ 5cells/μL in cerebrospinal fluid with presence of lymphoblasts)

Blue Advantage will treat **Kymriah™ (tisagenlecleucel)** as a **non-covered benefit** and as **investigational** when the above criteria are not met and for all other indications.

Effective for dates of service prior to January 1, 2018:

Blue Advantage will treat **adoptive immunotherapy**, using adoptive cellular therapy (ACT) for the administration of cytotoxic T-lymphocytes, cytokine-induced killer (CIK) cells, lymphokine-activated killer (LAK) cells, **chimeric antigen receptor therapy (CAR-T)**, tumor-infiltrating lymphocytes (TIL), or antigen-loaded autologous dendritic cells (ADC) as a **non-covered benefit** and as **investigational**.

Additional Policy Guidelines

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

The recommended dosage of Kymriah™ for patients 50 kg or less is 0.2 to 5.0×10^6 chimeric antigen receptor positive viable T cells per kg body weight intravenously; for patients above 50 kg, dose is 0.1 to 2.5 x 10^8 total chimeric antigen receptor positive viable T cells (non-weight-based) intravenously.

Central nervous system (CNS) disease for B-cell acute lymphoblastic leukemia is defined by the following groups:

- **CNS 1**: Absence of blasts on cerebrospinal fluid cytospin preparation, regardless of the white blood cell (WBC) count
- **CNS 2**: WBC count of less than 5/mL and blasts on cytospin findings
- **CNS 3**: WBC count of 5/mL or more and blasts on cytospin findings and/or clinical signs of CNS leukemia (e.g., facial nerve palsy, brain/eye involvement, hypothalamic syndrome)

Kymriah™ is available only through a restricted program under a risk evaluation and mitigation strategy (REMS) called the Kymriah REMS. The requirement for the REMS components are as follows:

- Health care facilities that dispense and administer Kymriah™ 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™ infusion, if needed for treatment of cytokine release syndrome.

- Certified health care facilities must ensure that health care providers, who prescribe, dispense or administer Kymriah™, are trained about the management of cytokine release syndrome and neurologic toxicities.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) is a malignancy 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. 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. In a 2017 meta-analysis of 20 studies of 11,249 pediatric ALL, the hazard ratio for event-free survival in MRD-negative patients compared with MRD-positive patients was 0.23 (95% confidence interval, 0.18 to 0.28).

Approximately 5000 cases of B-cell ALL are diagnosed every year in the United States, and approximately 620 pediatric and young adult patients with B-cell ALL will relapse each year in the United States. It is largely a disease of the young with approximately 60% of cases occurring in patients younger than 20 years old with a median age at diagnosis of 15 years. While it is treatable in 85% cases, approximately 15% of children and young adults with ALL will relapse while 2% to 3% of ALL patients are primary refractory. Retreatment of refractory or relapsed ALL is generally unsuccessful and associated with a high mortality rate. The 2-year survival rate among patients with ALL who relapse after hematopoietic cell transplantation is 15%. The Food and Drug Administration approved clofarabine (as a single agent or in combination) in 2004 and blinatumomab in 2014 for relapsed and refractory ALL. Reported median objective response

rates in the pivotal trials of the 2 agents were 19.7% and 33%, the median durations of response was 2.5 months and 6 months, and median overall survival durations were 3 months and 7.5 months, respectively. Note that the percentages of patients treated with 3 or more prior treatments of clofarabine and blinatumomab trial were 62% and 7%, respectively. Nevertheless, treatment options for patients with relapsed or refractory ALL are limited, associated with poor outcomes and high toxicity and the disease remains incurable.

Genetically Engineered T Cells

Peripheral T Lymphocytes

For individuals with cancers who receive autologous peripheral T lymphocytes containing tumor antigen-specific T-cell receptors, the evidence includes multiple small observational studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Multiple observational studies have examined autologous peripheral T lymphocytes containing tumor antigen-specific T-cell receptors in melanoma, Hodgkin and non-Hodgkin lymphoma, prostate tumors, and neuroblastoma. Because of the non-comparative nature of the available evidence with a small sample size, it is difficult to draw any meaningful conclusion. To establish efficacy, the following is needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

Tisagenlecleucel

For individuals who are 3 to 25 years of age with relapsed or refractory B-cell acute lymphoblastic leukemia who receive tisagenlecleucel, the evidence includes multiple single-arm prospective trials. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The pivotal single-arm trials 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 or 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 tisagenlecleucel were offset by a high frequency and severity of adverse reactions. Cytokine release syndrome 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 is required to assess the generalizability of tisagenlecleucel efficacy and safety outside of a clinical trial setting. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Pivotal Trial

In the pivotal phase 2 single-arm, international, multicenter trial, 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 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 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 a minimal residual disease [MRD]–negative bone marrow) within 3 months of receiving tisagenlecleucel. Key secondary end points were tested sequentially (after primary end point was significant) to control for overall type I errors.

Of 107 patients who were screened, 88 met the trial inclusion criteria and of these 68 (77.3%) were infused with tisagenlecleucel. In 7 (8%) patients, tisagenlecleucel could not be manufactured. The median time from enrollment to infusion was 44 days. Of the 68 patients, 63 patients received 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 tisagenlecleucel infusion. Patients also received protocol mandated lymphocyte-depleting chemotherapy 2 to 14 days prior to 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 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 of the Pivotal Study

Outcomes	Results, n (%) (95% confidence interval) or %
N	63
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)

Outcomes	Results, n (%) (95% confidence interval) or %
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 1/2a single-center study with 55 patients enrolled between March 2012 and November 2015. The ORR rate (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 multicentric study that enrolled 29 patients between August 2014 and February 2016. The ORR rate (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 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 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 tisagenlecleucel. Acquired hypogammaglobulinemia is an expected side effect of 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 tisagenlecleucel. It is unclear as to how long intravenous gamma globulin would be required.

Multiple design features of the 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 risk 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 the next 5 years, approximately 5000 patients may be enrolled in the first 5 years in a postmarketing registry that will follow patients up to 15 years after tisagenlecleucel infusion.

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

Serious Adverse Event[a]	Results, n (%)
N	68
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

Current National Comprehensive Cancer Network (NCCN) guidelines for acute lymphoblastic leukemia recommend (category 2A) tisagenlecleucel as a treatment option for:

- Philadelphia chromosome-positive patients 25 years or less in age with refractory disease or 2 or greater relapses and failure of 2 tyrosine kinase inhibitors.
- Philadelphia chromosome-negative patients 25 years or less in age with refractory disease or 2 or greater relapses and failure of 2 tyrosine kinase inhibitors.

Diffuse Large B-cell Lymphoma (DLBCL)

Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin lymphoma and accounts for approximately 25% of non-Hodgkin lymphoma cases. DLBCL exhibits large heterogeneity in morphologic, genetic, and clinical aspects and multiple clinicopathologic entities are defined by 2016 World Health Organization (WHO) classification that are sufficiently distinct to be considered separate diagnostic categories.

The efficacy and safety of tisagenlecleucel was evaluated in an open-label, multicenter, single-arm trial. Eligible patients were ≥ 18 years of age with relapsed or refractory DLBCL, who received ≥ 2 lines of chemotherapy, including rituximab and anthracycline, or relapsed following autologous hematopoietic stem cell transplantation (HSCT). 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), physician decision (n = 16), and adverse events (n = 3).

Of the 92 patients receiving tisagenlecleucel, 90% received physician's choice of bridging chemotherapy in the interval between start of screening and tisagenlecleucel infusion, among whom the median number of bridging chemotherapy regimens was 1 (range: 1 to 5) with 83% of patients receiving ≤ 2 regimens. A retrospectively identified sub-group of 68 patients was evaluable for the major efficacy outcome measures. Patients included in this sub-group had either had no bridging chemotherapy, or had imaging that showed measurable disease after completion of bridging chemotherapy, prior to tisagenlecleucel infusion. Of the 24 patients not included, 8 had no evidence of disease at baseline prior to tisagenlecleucel infusion, 15 did not have baseline imaging following bridging chemotherapy, and 1 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 (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 tisagenlecleucel infusion was 113 days (range: 47 to 196 days). The median dose was 3.5 × 108 CAR-positive

viable T cells (range: 1.0 to 5.2 × 108 cells). Seventy-three percent of patients received tisagenlecleucel in the inpatient setting.

Efficacy was established on the basis of complete response (CR) rate and duration of response (DOR), as determined by an independent review committee. The median time to first response to tisagenlecleucel (CR or PR) 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 1 month, 12 more by month 3, and the last by month 6 after tisagenlecleucel infusion.

Table 4. Response Rates in Relapsed or Refractory DLBCL in the JULIET Study

Response Rate	N=68
Overall Response Rate (ORR) (CR+PR), n (%)	34 (50%)
(95% CI)	(37.6%, 62.4%)
Complete Response Rate n (%)	22 (32%)
(95% CI)	(21.5%, 44.8%)
Partial Response Rate n (%)	12 (18%)
(95% CI)	(9.5%, 28.8%)

Summary: Tisagenlecleucel

For individuals who are 3 to 25 years of age with relapsed or refractory B-cell acute lymphoblastic leukemia who receive tisagenlecleucel, the evidence includes multiple single-arm prospective trials. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The pivotal single-arm trials 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 or 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 tisagenlecleucel were offset by a high frequency and severity of adverse reactions. Cytokine release syndrome was observed in more than half (63%) of the patients, and approximately 40% had an adverse event at grade 4 or higher.

Observed outcomes in a single-arm study design cannot be attributed solely to the intervention itself because they could occur as a result of a placebo effect, the natural course of the disease, or confounding by time-varying factors. However, it is unlikely that the 83% response rate (measured by CR or CRi) seen in the pivotal single-arm trial of tisagenlecleucel in patients with relapsed or refractory acute lymphoblastic leukemia could be the result of noninterventional effect. An unbiased estimate of the safety of tisagenlecleucel cannot be ascertained from this evidence base because of the lack of control arm, which makes it difficult to determine whether the observed adverse reactions are a consequence of background disease or the drug itself. However, tisagenlecleucel is a biologic drug and therefore observed adverse reactions that have immunologic basis are likely drug-mediated. The observed benefits seen with tisagenlecleucel were offset by a high frequency and severity of adverse reactions. 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 is required to assess the generalizability of tisagenlecleucel efficacy and safety outside of a clinical trial setting. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Key Words:

Tisagenlecleucel, Kymriah, chimeric antigen receptor therapy, CAR-T therapy, genetically engineered T-cells, gene therapy, acute lymphoblastic leukemia, b-cell lymphoma, diffuse large b-cell lymphoma, DLBCL

Approved by Governing Bodies:

On August 30, 2017, tisagenlecleucel (Kymriah™; Novartis) was approved by the Food and Drug Administration 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.

On May 1, 2018, tisagenlecleucel (Kymriah, Novartis™) was FDA approved for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

Current Coding:

CPT Codes:

Q2040	Tisagenlecleucel, up to 250 million car-positive T cells, including leukapheresis and dose preparation procedures, per infusion (**Effective 01/01/2018**)

Previous Coding:

CPT Codes:

J9999	Not otherwise classified, antineoplastic drugs [when specified as tisagenlecleucel]

References:

1. 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.

2. 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.
3. Food and Drug Administration (FDA). Hematology/Oncology (Cancer) Approvals & Safety Notificiations. Available at: www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm.
4. Food and Drug Administration (FDA). FDA Briefing Document: Oncologic Drugs Advisory Committee Meeting (BLA 125646,Tisagenlecleucel). n.d.; Available at: www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM566166.pdf.
5. Food and Drug Administration (FDA). FDA Presentations for the July 12, 2017 Meeting of the Oncologic Drugs Advisory Committee. 2017; Available at: www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM567383.pdf.
6. Humphries C. Adoptive cell therapy: Honing that killer instinct. Nature. Dec 19 2013; 504(7480):S13-15.
7. Hunger SP, Mullighan CG. Acute lymphoblastic leukemia in children. N Engl J Med. Oct 15 2015; 373(16):1541-1552.
8. 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.
9. Johnson LA, Morgan RA, Dudley ME, et al. Gene therapy with human and mouse T-cell receptors mediates cancer regression and targets normal tissues expressing cognate antigen. Blood. Jul 16 2009; 114(3):535-546.
10. 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.
11. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: Hodgkin lymphoma. Version 1.2017. Available at: www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf.
12. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: acute lymphoblastic leukemia. Version 4.2017. Available at: www.nccn.org/professionals/physician_gls/pdf/all.pdf.
13. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: b-cell lymphomas. Version 4.2018. Available at: www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf.
14. Novartis Briefing Document::Oncologic Drugs Advisory Committee Meeting (BLA 125646,Tisagenlecleucel). Available at: www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM566168.pdf.
15. Novartis Presentations for the July 12, 2017 Meeting of the Oncologic Drugs Advisory Committee (PDF - 2.6MB). Available at: www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM567385.pdf.
16. Novartis Pharmaceuticals Corporation. Kymriah (tisagenlecleucel). 2018. Available at: www.hcp.novartis.com/products/kymriah/

17. Ngo MC, Rooney CM, Howard JM, et al. Ex vivo gene transfer for improved adoptive immunotherapy of cancer. Hum Mol Genet. Apr 15 2011; 20(R1):R93-99.
18. Ochi T, Fujiwara H, Yasukawa M. Requisite considerations for successful adoptive immunotherapy with engineered T-lymphocytes using tumor antigen-specific T-cell receptor gene transfer. Expert Opin Biol Ther. Jun 2011; 11(6):699-713.
19. 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.
20. Rosenberg SA, Restifo NP, Yang JC, et al. Adoptive cell transfer: a clinical path to effective cancer immunotherapy. Nat Rev Cancer. Apr 2008; 8(4):299-308.
21. 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.
22. Till BG, Jensen MC, Wang J, et al. Adoptive immunotherapy for indolent non-Hodgkin lymphoma and mantle cell lymphoma using genetically modified autologous CD20-specific T cells. Blood. Sep 15 2008; 112(6):2261-2271.
23. 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.

Policy History:

Adopted for Blue Advantage, December 2017
Medical Policy Group, December 2017
Available for comment January 9, 2018 to February 24, 2018
Comment period extended to March 9, 2018.
Medical Policy Group, April 2018
Medical Policy Group, May 2018
Available for comment May 21 through June 31, 2018
