

EFFECTIVE DATE: 06|01|2018
POLICY LAST UPDATED: 06|04|2019

OVERVIEW

KYMRIA[™] (tisagenlecleucel) is a prescription cancer treatment used in patients up to 25 years old who have acute lymphoblastic leukemia (ALL) that is either relapsing (went into remission, then came back) or refractory (did not go into remission with other leukemia treatments). KYMRIA is made from your own white blood cells.

This policy is applicable to BlueCHiP for Medicare products only. For Commercial Products, see related policy section

MEDICAL CRITERIA

BlueCHiP for Medicare

KYMRIA[™] (tisagenlecleucel) will be approved when ALL of the following are met:

1. ONE of the following:
 - A. The patient has a diagnosis of relapsed/refractory B-cell precursor acute lymphoblastic leukemia (ALL) (note: the patient must meet all aspects of the diagnosis as indicated) and ALL of the following:
 - i. The patient is 25 years of age or younger
AND
 - ii. BOTH of the following:
 1. ONE of the following:
 - a. The patient did not achieve complete response (CR) following 2 cycles of standard chemotherapy
OR
 - b. The patient is in the second or later relapse following treatment with 2 or more cycles of standard chemotherapy
AND
 2. If the patient is Philadelphia Chromosome positive (Ph+), ONE of the following:
 - a. The patient has failed treatment with 2 or more tyrosine kinase inhibitors (TKI) indicated for ALL
OR
 - b. The patient has intolerance, hypersensitivity, or contraindications to all TKI agents indicated for ALL
 - B. The patient has a diagnosis of Relapsed or refractory large B-cell lymphoma [including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma] AND ALL of the following:
 - i. The patient is an adult
AND
 - ii. The patient has NOT had a previous allogeneic hematopoietic stem cell transplant
AND
 - iii. The patient has an ejection fraction \geq 45%
AND

- iv. The patient has a creatinine clearance ≥ 60 mL/min
AND
- v. The patient has an absolute lymphocyte concentration $\geq 300/\mu\text{L}$
AND
- vi. ONE of the following:
 - 1. The patient did not achieve complete response (CR) following 2 cycles of standard chemotherapy
OR
 - 2. The patient is in the second or later relapse following treatment with 2 or more cycles of standard chemotherapy

AND

- 2. The prescriber has confirmed the patient has CD19 tumor expression
AND
- 3. The patient does not have active uncontrolled infection including Hepatitis B, Hepatitis C, or HIV infection
AND
- 4. The patient does not have active central nervous system (CNS) malignancy involvement (i.e. white blood cell (WBC) count greater than or equal to 5 cells/mcl in the cerebral spinal fluid (CSF) with presence of lymphoblasts)
AND
- 5. The patient does not have any FDA labeled contraindications to the requested agent
AND
- 6. The patient has not previously been treated with gene therapy including the requested agent

Approval: 1 treatment course per lifetime

PRIOR AUTHORIZATION

Prior authorization is required for BlueCHiP for Medicare.

POLICY STATEMENT

BlueCHiP for Medicare

KYMRIAH (tisagenlecleucel) is medically necessary when the above criteria has been met

Note: Blue Cross and Blue Shield of Rhode Island reserves the right to request information from the provider regarding the member's response to the therapy. Failure to agree may result in denial of the request. Provider agrees to provide documentation of response upon request.

COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for applicable physician administered infusion drug benefits/coverage.

BACKGROUND

Acute Lymphoblastic Leukemia(ALL) is characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs.³The incidence of ALL in the united states is 1.58 cases per 100,000 individuals per year and the median age at diagnosis is 15 years.³ Risk factors for developing ALL include older age (over 70 years), exposure to chemotherapy or radiation, and presence of genetic disorders (e.g. Down syndrome). A diagnosis of ALL can be made when there is demonstration of greater than or equal to 20% bone marrow lymphoblasts upon hematopathology review of bone marrow aspirate. Following the diagnosis of ALL, a genetic characterization (e.g. determining presence of Philadelphia chromosome) is completed to aid in optimal risk stratification and treatment planning. Immunophenotypic classification of ALL should also be completed. Acute lymphoblastic leukemia can be classified into the following 3 groups based on immunophenotype: precursor B-cell ALL, mature B-cell ALL, and T-cell ALL. Tisagenlecleucel is indicated for precursor B-cell ALL.

Treatment of ALL represents one of the most complex and intensive programs in cancer therapy.³ Initial treatment includes induction therapy with a combination of vincristine, anthracyclines (e.g. daunorubicin, doxorubicin), and corticosteroids with or without L-asparaginase and/or cyclophosphamide. Additionally, intrathecal antimetabolites such as methotrexate, cytarabine, and/or 6-mercaptopurine are often included at induction therapy for CNS prophylaxis. The goal of induction therapy is to achieve complete remission (CR). Patients who do not achieve CR following induction therapy are considered to have primary refractory disease. 15% of ALL patients fall within this category. For patients who achieve CR, postinduction consolidation therapy followed by maintenance therapy is recommended.

Treatment options for patients who have primary refractory ALL or have relapsed following initial or subsequent CR may be managed using repeat chemotherapy (in combination with tyrosine kinase inhibitor for patients who are Philadelphia Chromosome positive), blinatumomab, or tisagenlecleucel (for refractory ALL or second or later relapsed ALL).

Diffuse Large B-cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is a subtype of non-Hodgkin lymphomas (NHL). DLBCL are the most common lymphoid neoplasms in adults, accounting for approximately 32.5% of NHLs diagnosed annually. Immunophenotypic analysis is essential for the differentiation of the various subtypes of NHL to establish the proper diagnosis. This can be performed by flow cytometry and/or immunohistochemistry (IHC). NCCN lists the following as essential diagnostic testing in DLBCL:

- Adequate immunophenotyping to establish diagnosis and germinal center B-cell (GCB) subtype or non-GCB origin
- IHC panel: CD20, CD3, CD5, CD10, CD45, BCL2, BCL6, Ki-67, ORF4/MUM1, MYC with or without cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD3, CD5, CD19, CD10, CD20

Follicular lymphoma is another subtype of NHL. About 3% of patients with follicular lymphoma will have histological transformation to DLBCL. This transformation is generally associated with a poor clinical outcome.

KYMRIA (tisagenlecleucel)

Tisagenlecleucel is an antigen-specific autologous immunotherapy comprising of T cells that have been genetically-modified to target cells that express CD19. CD19 is an antigen expressed on the surface of B-cells and tumors derived from B-cells. The tisagenlecleucel chimeric antigen receptor (CAR) protein consists of an extracellular portion that has a murine anti-CD-19 single chain antibody fragment and an intracellular portion that contains T cell signaling and co-stimulatory domains. The intracellular domains play critical roles in tisagenlecleucel's functions including T cell activation and anti-tumor activity.

Diagnosis of ALL requires demonstration of equal to or greater than 20% bone marrow lymphoblasts on a hematology review of bone marrow aspirate

Efficacy

The efficacy of tisagenlecleucel is based on results of a phase 2, open label, multicenter single-arm trial in pediatric and young adult patients with refractory/relapsed (R/R) B-cell precursor ALL. The trial enrolled patients who had primary refractory disease (defined as failure to achieve complete response after two cycles of standard chemotherapy) or had two or more relapses. Key exclusion criteria included history of prior treatment with any gene therapy, presence of CNS involvement as defined by NCCN guidelines (i.e. white blood cell (WBC) count greater than or equal to 5 cells/mcl in the cerebral spinal fluid (CSF) with presence of lymphoblasts), and presence of active infection including hepatitis B, hepatitis C, and HIV.

The trial enrolled 88 patients of whom 63 received a single dose of tisagenlecleucel and were therefore evaluable for efficacy. The 63 evaluable patients included 6 patients (10%) patients who had primary refractory disease, 30 patients (48%) who had one prior stem cell transplantation, and 5 patients (8%) had two stem cell transplantations. Of the 63 patients, 35 patients were males and 28 patients were females. The median age was 12 years (range, 3-23 years). Seventy-three percent of patients were white, 10% were Asian, and 17% were of other races. All 63 evaluable patients received tisagenlecleucel that was manufactured at the manufacturer's United States facility.

The primary endpoint of the trial was overall remission rate (ORR), defined as a best overall response rate (BOR) of complete remission (CR) or complete remission with incomplete blood count recovery (CRi) assessed within 3 months following the infusion of tisagenlecleucel. The trial also evaluated the duration of CR, proportion of patients with CR and minimal residual disease (MRD). Among the 63 infused patients, 52 (83%) achieved CR/CRi, all of which were MRD-negative. With a median follow-up of 4.8 months from response, the median duration of CR/CRi was not reached (range: 1.2 to 14.1+ months). Median time to onset of CR/CRi was 29 days with onset of CR/CRi between 26 and 31 days for 50/52 (96%) responders. The stem cell transplantation rate among those who achieved CR/CRi was 12% (6/52).

Safety

The most common adverse events associated with tisagenlecleucel are cytokine release syndrome (CRS), hypogammaglobulinemia, infectious-pathogens, pyrexia, decreased appetite, headache, encephalopathy, hypotension, bleeding episodes, tachycardia, nausea, diarrhea, vomiting, viral infectious disorders, hypoxia, fatigue, acute kidney injury, and delirium. Tisagenlecleucel carries a boxed warning for CRS and neurological toxicities. The labeling also recommends against administering tisagenlecleucel in patients with active infection or inflammatory disorders. Given its safety profile, tisagenlecleucel is available only through a restricted program under the Kymriah Risk Evaluation and Mitigation Strategy (REMS). The goals of the Kymriah REMS program are as follows:

1. Ensure that hospitals and their associated clinics that dispense tisagenlecleucel are specially certified and have on-site, immediate access to tocilizumab.
2. Ensure those who prescribe, dispense, or administer tisagenlecleucel are aware of how to manage the risks of CRS and neurological toxicities.

CODING

The following code is medically necessary when the criteria is met.

Note: To ensure correct claims processing, the claim **must be filed** with the HCPCS below and the NDC number. This is necessary as the NDC's have different reimbursement rates.

Q2042 Tisagenlecleucel, up to 600 million CAR-positive viable T cells, including leukapheresis and dose preparation procedures, per therapeutic dose

RELATED POLICIES

Prior Authorization of Drugs

PUBLISHED

Provider Update, August 2019

Provider Update, June 2018

Provider Update, December 2017

REFERENCES:

1. Kymriah prescribing information. Novartis. May 2018.
2. Kymriah Risk Evaluation and Mitigation Strategy (REMs)

3. NCCN Acute Lymphoblastic Leukemia treatment guidelines. Version 3.2017 – September 2017.
Accessed September 2017.
4. NCCN B-cell Lymphomas guidelines version 3.2018. Accessed May 2018.
5. KYMRIATM (tisagenlecleucel)

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