POLICY: Oncology – Kymriah® (tisagenlecleucel suspension for intravenous infusion – Novartis Oncology)

APPROVAL DATE: 04/24/2019

OVERVIEW

Kymriah, a CD19-directed genetically modified autologous T cell immunotherapy, is indicated 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.[1] Kymriah is also indicated 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) not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. Regarding this specific indication, Kyrmiah is not indicated for treatment of patients with primary central nervous system lymphoma.[1] Kymriah has a Boxed Warning regarding cytokine release syndrome (CRS) and neurological toxicities. Due to these risks, Kymriah is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Kymriah REMS.[1]

Kymriah is supplied as a frozen suspension of genetically modified autologous T cells in infusion bag(s) labeled for the specific recipient.[1] Kymriah is shipped directly to the cell laboratory associated with the infusion center in a liquid nitrogen Dewar. The product and patient-specific labels are found inside the Dewar. Store the infusion bag in the vapor phase of liquid nitrogen (less than or equal to minus 120°C) in a temperature-monitored system. Kymriah should be thawed prior to infusion.

Clinical Efficacy

The efficacy of Kymriah in pediatric and young adults with relapsed or refractory B-cell precursor ALL was assessed in an open-label, multicenter, single-arm study called ELIANA.[1-2] Therapy consisted of lymphodepleting chemotherapy (fludarabine 30 mg/m^2 daily for 4 days and cyclophosphamide 500 mg/m^2 daily for 2 days) followed by a single Kymriah dose.[1-2] Among the 63 patients who were evaluable for efficacy in the Kymriah prescribing information, 83% of patients achieved complete remission or complete remission with incomplete blood count recovery.[1] The published study evaluated 75 patients and the overall remission rate (the rate of complete remission or complete remission with incomplete hematologic recovery) within 3 months was 81%.[2] The efficacy of Kymriah was assessed in an open-label, multicenter, single-arm trial called JULIET.[1,3] Patients were ≥ 18 years of age with relapsed or refractory DLBCL who had previously received at least two lines of chemotherapy (including Rituxan® [rituximab injection for intravenous use] and an anathracycline), or relapsed following autologous hematopoietic stem cell transplantation (HSCT).[1] A single Kymriah infusion was administered after 2 to 11 days following the completion of lymphodepleting chemotherapy which involved fludarabine and cyclophosphamide, or Treanda® (bendamustine injection for intravenous use). Lymphodepleting chemotherapy was not required if the patient's white blood cell count was < 1,000 cells/μL. In total, 160 patients were enrolled and 106 patients received Kymriah; 92 patients received product that was manufactured in the US. The efficacy evaluation population included 68 patients and the overall response rate was 50% (n = 34/68).

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for ALL (version 2.2019 – April 5, 2019) address Kymriah.[4,5] In Philadelphia chromosome-positive B-cell ALL, Kymriah is cited as a treatment option for patients < 26 years of age and with refractory disease or ≥ two relapses and failure of two tyrosine kinase inhibitors (TKIs) [category 2A]. For Philadelphia chromosome-negative B-cell ALL, Kymriah is listed as a therapy option for patients < 26 years of age and with refractory disease or ≥ two relapses (category 2A).

The NCCN guidelines for B-cell lymphomas (version 2.2019 – March 6, 2019) recommend Kymriah for the treatment of the following relapsed or refractory disease after at least two course of systemic therapy: DLBCL following transformation from follicular lymphoma, DLBCL, high-grade B-cell lymphoma, AIDS-related B-cell lymphoma, and post-transplant lymphoproliferative disorders (category 2A).[5,6]

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Kymriah. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s).

Due to the specialized skills required for evaluation and diagnosis of patients treated with Kymriah, as well as the monitoring required for adverse events and long-term efficacy, approval requires Kymriah to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals for initial therapy are provided for the initial approval duration noted below.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Kymriah is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. Acute Lymphoblastic Leukemia, B-Cell Precursor. Approve a single dose if the patient meets the following criteria (A, B, C, D, and E):

A) The patient is < 26 years of age; AND
B) Kymriah is prescribed by or in consultation with an oncologist; AND
C) Kymriah is being used for disease that is refractory, or in second or later relapse; AND
D) The patient received lymphodepleting chemotherapy prior to Kymriah infusion; AND
E) The patient has not been previously treated with Kymriah.

Dosing in Acute Lymphoblastic Leukemia.
Dosing must meet the following (A or B):[1]

A) Administer 0.2 to 5.0 x 10^6 chimeric antigen receptor (CAR)-positive viable T cells per kg body weight intravenously for patients ≤ 50 kg; OR
B) Administer 0.1 to 2.5 x 10^8 CAR-positive viable T-cells intravenously for patients > 50 kg.

Kymriah is provided in a single-dose unit containing CAR-positive viable T cells. The dose for patients ≤ 50 kg is 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg body weight. The dose for patients > 50 kg is 0.1 to 2.5 x 10^8 CAR-positive viable T cells.

2. B-Cell Lymphoma. Approve a single dose if the patient meets the following criteria (A, B, C, D, E, and F):

A) The patient meets one of the following diagnosis (i, ii, iii, iv, v, vi, vii or viii):
i. Large B-cell lymphoma; OR
ii. Diffuse large B-cell lymphoma; OR
iii. Primary mediastinal large B-cell lymphoma; OR
iv. High-grade B-cell lymphoma; OR
v. Diffuse large B-cell lymphoma arising from follicular lymphoma;
vi. AIDS-related B-cell lymphoma; OR

vii. Human Herpes Virus 8-positive diffuse large B-cell lymphoma; OR
viii. Post-transplant lymphoproliferative disorders, B-cell type; AND

B) The patient is ≥ 18 years of age; AND
C) Kymriah is prescribed by or in consultation with an oncologist; AND
D) Kymriah is being used for disease that is relapsed, or refractory after two or more lines of systemic therapy; AND
E) The patient must meet one of the following (i or ii):
  i. The patient received lymphodepleting chemotherapy prior to Kymriah infusion; OR
  ii. The patient's white blood cell count is less than or equal to 1 x 10^9/L within 1 week prior to Kymriah infusion: AND
F) The patient has not been previously treated with Kymriah.

Dosing in B-Cell Lymphomas.
Dosing must meet the following: The dose is 0.6 to 6.0 x 10^8 chimeric antigen receptor (CAR)-positive viable T cells administered intravenously.[1]

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Kymriah has not been shown to be effective or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Re-treatment with Kymriah.** Kymriah is for one time use, repeat dosing is not approvable.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Kymriah™ suspension for intravenous infusion [prescribing information]. East Hanover, NJ: Novartis Oncology; May 2018.
2. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med*. 2018;378:439-448.
3. Schuster SJ, Bishop MR, Tam CS, et al. Primary analysis of Juliet: a global, pivotal, phase 2 trial of CTL019 in adult patients with relapsed or refractory diffuse large b-cell lymphoma. *Blood*. 2017;130(Suppl 1):577. Available at: http://www.bloodjournal.org/content/130/Suppl_1/577. Accessed on June 4, 2018.
4. The NCCN Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (Version 2.2019 – April 5, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on April 9, 2019.
5. The NCCN Drugs and Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on April 9, 2019. Search term: tisagenlecleucel.
6. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 2.2019 – March 6, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on April 9, 2019.

HISTORY

Type of Revision	Summary of Changes*	Approval Date
New Policy	-	04/25/2018
Selected revision	Added criteria for a new indication regarding B-cell lymphoma.	06/06/2018
Annual Revision	**Acute Lymphoblastic Leukemia:** Add the descriptor of "B-cell Precursor" to the condition of approval. Criteria were added such that the lifetime therapy is for one dose. **B Cell Lymphoma:** The following indications were added to the B-cell lymphoma criteria: Primary mediastinal large B-cell lymphoma, AIDS-related B-cell lymphoma, human herpes virus 8-	04/24/2019

	positive diffuse large B-cell lymphoma, and post-transplant lymphoproliferative disorder. Criteria were added such that the lifetime therapy is for one dose.	