Policy:	**Oncology (Injectable – CAR-T) – Kymriah Utilization Management Medical Policy** • Kymriah® (tisagenlecleucel intravenous infusion – Novartis Oncology)
Date:	07/26/2023
Applicable Lines of Business:	Medicare Advantage - Medical
Applicable States:	All States

OVERVIEW

Kymriah, a CD19-directed genetically modified autologous T cell immunotherapy, is indicated for the following uses:[1]

- **B-cell precursor acute lymphoblastic leukemia** (ALL), in patients ≤ 25 years of age with disease that is refractory or in second or later relapse.
- **Follicular lymphoma**, in patients ≥ 18 years of age with relapsed or refractory disease after two or more lines of systemic therapy. This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).
- **Large B-cell lymphoma**, in patients ≥ 18 years of age with relapsed or refractory disease 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: Kymriah is not indicated for treatment of patients with primary central nervous system lymphoma.

Kymriah, a chimeric antigen receptor T-cell (CAR-T) therapy, 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.

Guidelines

Kymriah is discussed in guidelines from The National Comprehensive Cancer Network (NCCN).

- **ALL, adult:** The NCCN guidelines (version 1.2022 – April 4, 2022) address Kymriah.[2,3] 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).
- **ALL, pediatric:** The NCCN guidelines (version 2.2023 – March 10, 2023) recommend Kymriah for the treatment of patients with refractory or ≥ two relapses, TKI intolerant or refractory disease, or relapse post-hematopoietic stem cell transplantation (category 2A).[3,5] Kymriah is also recommended for patients who are minimal residual disease positive after consolidation therapy, and in Philadelphia chromosome-positive disease with less than complete response.

- **B-cell lymphoma:** The NCCN guidelines (version 2.2023 – February 8, 2023) recommend Kymriah for the treatment of the following relapsed or refractory disease after at least two course of systemic therapy: DLBCL, DLBCL following transformation from follicular lymphoma or nodal marginal zone lymphoma, follicular lymphoma, high-grade B-cell lymphoma, human immunodeficiency virus (HIV)-related B-cell lymphoma, human herpes virus 8 (HHV8)-positive DLBCL, primary effusion lymphoma, and post-transplant lymphoproliferative disorders (category 2A).[3,4]

Safety

Kymriah has a Boxed Warning regarding cytokine release syndrome and neurological toxicities.[1] Due to these risks, Kymriah is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Kymriah REMS.

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). The approval duration is 6 months to allow for an adequate time frame to prepare and administer 1 dose of therapy.

This policy incorporates Medicare coverage guidance as set forth in National Coverage Determinations (NCDs) and Local Coverage Determinations (LCDs), as well as in companion policy articles and other guidance applicable to the relevant service areas. These documents are cited in the References section of this policy. In some cases, this guidance includes specific lists of HCPCS and ICD-10 codes to help inform the coverage determination process. The Articles that include specific lists for billing and coding purposes will be included in the Reference section of this policy. However, to the extent that this policy cites such lists of HCPCS and ICD-10 codes, they should be used for reference purposes only. The presence of a specific HCPCS or ICD-10 code in a chart or companion article to an LCD is not by itself sufficient to approve coverage. Similarly, the absence of such a code does not necessarily mean that the applicable condition or diagnosis is excluded from coverage.

Note: Conditions for coverage outlined in this Medicare Advantage Medical Policy may be less restrictive than those found in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles. Examples of situations where this clinical policy may be less restrictive include, but are not limited to, coverage of additional indications supported by CMS-approved compendia and the exclusion from this policy of additional coverage criteria requirements outlined in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles.

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.

Criteria. Approve a single dose if the patient meets the following criteria (A, B, C, and D):

A) The patient is < 26 years of age; AND
B) The patient meets one of the following (i, ii, or iii):
- **i.** The patient has disease that is refractory, or in second or later relapse; OR
- **ii.** The patient is minimal residual disease positive after consolidation therapy; OR
- **iii.** The patient is Philadelphia chromosome-positive and has experienced one of the following (a, b, or c):
  - **a)** Less than complete response; OR
  - **b)** Tyrosine kinase inhibitor intolerant or refractory disease; OR
    Note: Tyrosine kinase inhibitors include Sprycel® (dasatinib tablets), imatinib tablets, Iclusig® (ponatinib tablets), Tasigna® (nilotinib capsules), and Bosulif® (bosutinib tablets).
  - **c)** Relapse post-hematopoietic stem cell transplantation; AND

C) The patient received or plans to receive lymphodepleting chemotherapy prior to Kymriah infusion; AND
D) The patient has not been previously treated with CAR-T therapy.
Note: Examples of CAR-T therapy include Kymriah, Breyanzi® (lisocabtagene maraleucel injection), Tecartus™ (brexucabtagene autoleucel injection), Yescarta® (axicabtagene ciloleucel injection), and Abecma® (idecabtagene vicleucel injection).

Dosing. Approve one of the following dosing regimens (A or B):
A) The dose is up 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) The dose is up to 2.5 x 10^8 CAR-positive viable T-cells intravenously for patients > 50 kg.

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2. B-Cell Lymphoma.

Criteria. Approve a single dose if the patient meets the following criteria (A, B, C, D, and E):
A) The patient has one of the following diagnoses (i, ii, iii, iv, v, vi, vii, viii, ix or x):
- **i.** Large B-cell lymphoma; OR
- **ii.** Diffuse large B-cell lymphoma; OR
- **iii.** High-grade B-cell lymphoma; OR
- **iv.** Diffuse large B-cell lymphoma arising from follicular lymphoma; OR
- **v.** Follicular lymphoma; OR
- **vi.** Diffuse large B-cell lymphoma arising from nodal marginal zone lymphoma; OR
- **vii.** Human immunodeficiency virus (HIV)-related B-cell lymphoma; OR
- **viii.** Human Herpes Virus 8-positive diffuse large B-cell lymphoma; OR
- **ix.** Primary effusion lymphoma; OR
- **x.** Post-transplant lymphoproliferative disorders, B-cell type; AND

B) The patient is ≥ 18 years of age; AND
C) Kymriah is being used for disease that is relapsed, or refractory after two or more lines of systemic therapy; AND
D) The patient must meet one of the following (i or ii):
- **i.** The patient received or plans to receive 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

E) The patient has not been previously treated with CAR-T therapy.

Note: Examples of CAR-T therapy include Kymriah, Breyanzi® (lisocabtagene maraleucel injection), Tecartus™ (brexucabtagene autoleucel injection) Yescarta® (axicabtagene ciloleucel injection), and Abecma® (idecabtagene vicleucel injection).

Dosing. The dose is up to 6.0 x 10^8 chimeric antigen receptor (CAR)-positive viable T cells administered intravenously.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Kymriah is not recommended in the following situations:

1. 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™ intravenous infusion [prescribing information]. East Hanover, NJ: Novartis Oncology; May 2022.
2. The NCCN Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (version 1.2022 – April 4, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 20, 2023.
3. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 20, 2023. Search term: tisagenlecleucel.
4. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 2.2023 – February 8, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 20, 2023.
5. The NCCN Pediatric Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (version 2.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 20, 2023.
6. Centers for Medicare and Medicaid Services. National Coverage Determination (NCD) for Chimeric Antigen Receptor (CAR) T-cell Therapy (110.24). Original effective date 8/7/2019. Implementation date 2/16/2021. Accessed July 26, 2023.

HISTORY

Type of Revision	Summary of Changes*	Date
New Policy	New Medicare Advantage Medical Policy	10/09/2019
Policy revision	Non-clinical update to policy to add the statement "This policy incorporates Medicare coverage guidance as set forth in National Coverage Determinations (NCDs) and Local Coverage Determinations (LCDs), as well as in companion policy articles and other guidance applicable to the relevant service areas. These documents are cited in the References section of this policy. In some cases, this guidance includes specific lists of HCPCS and ICD-10 codes to help inform the coverage determination process. The Articles that include specific lists for billing and coding purposes will be included in the Reference section of this policy. However, to the extent that this policy cites such lists of HCPCS and ICD-10 codes, they should be used for reference purposes only. The presence of a specific HCPCS or ICD-10 code in a chart or companion article to an LCD is not by itself sufficient to approve coverage. Similarly, the absence of such a code does not necessarily mean that the applicable condition or diagnosis is excluded from coverage."	1/30/2020
Policy revision	Added the following to the Policy Statement "Note: Conditions for coverage outlined in this Medicare Advantage Medical Policy may be less restrictive than those found in applicable National Coverage	04/03/2020

	Determinations, Local Coverage Determinations and/or Local Coverage Articles. Examples of situations where this clinical policy may be less restrictive include, but are not limited to, coverage of additional indications supported by CMS-approved compendia and the exclusion from this policy of additional coverage criteria requirements outlined in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles."	
Policy revision	**Acute Lymphoblastic Leukema:** Added additional criteria for approval including minimal residual disease positive after consolidation therapy; and for Philadelphia chromosome-positive disease – less than complete response, high-risk genetics, tyrosine kinase inhibitor intolerant or refractory disease, and relapse post-hematopoietic stem cell transplant. **B-cell lymphoma:** Added approval criteria for diffuse large B-cell lymphoma arising from nodal marginal zone lymphoma. Revised criteria to not allow previous treatment with Yescarta.	05/04/2020
Policy revision	**Acute Lymphoblastic Leukemia:** "High risk genetics' was removed from criterion for patients with Philadelphia chromosome-positive ALL. Revised criterion: Patient has not been previously treated with Kymriah or Yescarta, to: Patient has not been previously treated with CAR-T therapy. Added Note listing all CAR-T therapies. **B-Cell Lymphoma:** Removed primary mediastinal large B-cell lymphoma from listed of diagnoses. Revised criterion: Patient has not been previously treated with Kymriah or Yescarta, to: Patient has not been previously treated with CAR-T therapy. Added Note listing all CAR-T therapies. **Conditions Not Recommended for Approval:** Removed criterion for Retreatment with Kymriah (not needed since addressed in criteria section).	04/14/2021
Policy revision	**Acute Lymphoblastic Leukemia:** Added "or plan to receive" to the requirement that the patient received lymphodepleting chemotherapy prior to Kymriah infusion. Also, for the criterion "The patient has not been previously treated with CAR-T therapy" – added Abecma to the list of examples of CAR-T therapy. **B-Cell Lymphoma:** Added "or plan to receive" to the requirement that the patient received lymphodepleting chemotherapy prior to Kymriah infusion. Also, for the criterion "The patient has not been previously treated with CAR-T therapy" – added Abecma to the list of examples of CAR-T therapy.	01/14/2022
Policy revision	**B- Cell Lymphoma:** Added follicular lymphoma as an additional option for approval.	06/30/2022
Policy revision	**B-Cell Lymphoma:** Primary effusion lymphoma was added as an additional option for approval. Acquired immune deficiency syndrome (AIDS)-related B-cell lymphoma was changed to human immunodeficiency virus (HIV)-related B-cell lymphoma.	05/01/2023
Policy revision	Added: "The approval duration is 6 months to allow for an adequate time frame to prepare and administer 1 dose of therapy." to the Policy Statement	07/26/2023