Utilization Review Policy 169

POLICY: Oncology (Injectable – CAR-T) – Kymriah Utilization Management Medical Policy
- Kymriah® (tisagenlecleucel intravenous infusion – Novartis Oncology)

EFFECTIVE DATE: 1/1/2021
LAST REVISION DATE: 03/25/2025

COVERAGE CRITERIA FOR: All Aspirus Medicare Plans

SUMMARY OF EVIDENCE

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 3.2024 – December 20, 2024) 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 2.2025 – December 16, 2024) recommend Kymriah for the treatment of patients with BCR::ABL1-negative (Philadelphia chromosome-

negative) ALL that is refractory or ≥ two relapses; and for BCR::ABL1-positive (Philadelphia chromosome-positive) ALL that is TKI intolerant or refractory, or relapsed 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 BCR::ABL1-positive disease with less than complete response (category 2B).

- **B-cell lymphoma:** The NCCN guidelines (version 2.2025 – February 10, 2025) 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 indolent 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, neurological toxicities, and secondary hematological malignancies.[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.

ANALYSIS OF EVIDENCE

The information provided in the summary of evidence is supported by labeled indications, CMS-approved compendia, published clinical literature, clinical practice guidelines, and/or applicable National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs). Refer to the Sources of Information section of this policy for additional information.

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 Sources of Information 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 Sources of Information 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.

Indications with a ^ below are referenced in both the corresponding Standard Medical Utilization Management Internal Policy AND applicable National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), and/or Local Coverage Articles (LCAs). Coverage criteria for these indications may be internally developed and/or referenced in applicable NCDs, LCDs, and/or LCAs. For these indications, internally developed coverage criteria is denoted throughout the policy in the following manner: 1) IC-L (internal criteria supported by the labeled indication), 2) IC-COMP (internal criteria supported by CMS-approved compendia), 3) IC-ISGP (internal criteria intended to interpret or supplement general provisions outlined in applicable NCDs, LCDs, and/or LCAs), or 4) IC-EC (internal criteria intended to expand coverage beyond the coverage outlined in applicable NCDs, LCDs, and/or LCAs). For these indications, coverage criteria that is NOT denoted with one of the above indicators is referenced in applicable NCDs, LCDs, and/or LCAs. Additional information supporting the rationale for determination of internal coverage criteria can be found via the Sources of Information section.

Indications with a @ below are referenced in the corresponding Standard Medical Utilization Management Internal Policy, but are NOT directly referenced in applicable National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), and/or Local Coverage Articles (LCAs). Coverage criteria for these indications is internally developed. These indications and their respective coverage criteria represent expanded coverage beyond the coverage outlined in applicable NCDs, LCDs, and/or LCAs.

Indications with a # below are supported and referenced in applicable National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), and/or Local Coverage Articles (LCAs), but are NOT directly referenced in the corresponding Standard Medical Utilization Management Internal Policy. Coverage criteria for these indications is referenced in applicable NCDs, LCDs, and/or LCAs.

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; IC-COMP AND
B) The patient meets one of the following (i, ii, or iii):
   a. The patient has disease that is refractory, or in second or later relapse; IC-COMP OR
   b. The patient is minimal residual disease positive after consolidation therapy; IC-COMP OR
   c. The patient is Philadelphia chromosome-positive and has experienced one of the following (a, b, or c): IC-COMP
      i. Less than complete response; IC-COMP OR
      ii. Tyrosine kinase inhibitor intolerant or refractory disease; IC-COMP OR

Note: Tyrosine kinase inhibitors include Sprycel® (dasatinib tablets), imatinib tablets, Iclusig® (ponatinib tablets), Tasigna® (nilotinib capsules), and Bosulif® (bosutinib tablets).

iii. Relapse post-hematopoietic stem cell transplantation; IC-COMP AND

C) The patient received or plans to receive lymphodepleting chemotherapy prior to Kymriah infusion; IC-COMP AND

D) The patient has not been previously treated with CAR-T therapy. IC-COMP
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, and D):

A) Patient is ≥ 18 years of age; IC-COMP AND

B) Patient meets ONE of the following (i or ii):

a. Patient meets BOTH of the following (a and b):
   1. Patient has follicular lymphoma; IC-COMP AND
   2. Medication is used for relapsed or refractory disease after two or more lines of systemic therapy; IC-COMP OR
      Note: Examples of systemic therapy include CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + Gazyva (obinutuzumab intravenous infusion) or rituximab products, CVP (cyclophosphamide, vincristine, prednisone) + rituximab products, lenalidimide + rituximab products.

b. Patient meets BOTH of the following (a and b):
   1. The patient has one of the following diagnoses [(1), (2), (3), (4), (5), (6), (7), (8), or (9)]:
      a. Large B-cell lymphoma; IC-COMP OR
      b. Diffuse large B-cell lymphoma; IC-COMP OR
      c. High-grade B-cell lymphoma; IC-COMP OR
      d. Diffuse large B-cell lymphoma arising from indolent lymphoma; IC-COMP OR
      e. Human immunodeficiency virus (HIV)-related B-cell lymphoma; IC-COMP OR
      f. HIV-related plasmablastic lymphoma; IC-COMP OR
      g. Human Herpes Virus 8-positive diffuse large B-cell lymphoma; IC-COMP OR
      h. Primary effusion lymphoma; IC-COMP OR
      i. Post-transplant lymphoproliferative disorders, B-cell type; IC-COMP AND
   2. Medication is used in ONE of the following situations [(1) or (2)]:
      a. Disease that is relapsed or refractory after two or more lines of systemic therapy; IC-COMP OR

Note: Examples of systemic therapy include RCHOP (rituximab product, cyclophosphamide, doxorubicin, vincristine, prednisone), dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab product, DHA (dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) ± rituximab product.

b. Disease relapse > 12 months after first-line therapy and partial response to second-line therapy; IC-COMP AND
Note: Examples of systemic therapy include RCHOP (rituximab product, cyclophosphamide, doxorubicin, vincristine, prednisone), dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab product, RCDOP (rituximab product, cyclophosphamide, liposomal doxorubicin, vincristine, prednisone).

C) Patient meets ONE of the following (i or ii):
- **i.** The patient received or plans to receive lymphodepleting chemotherapy prior to Kymriah infusion; IC-COMP 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; IC-COMP AND

D) The patient has not been previously treated with chimeric antigen receptor T-cell (CAR-T) therapy. IC-COMP
Note: Examples of CAR-T therapy includes Kymriah, Breyanzi (lisocabtagene maraleucel intravenous infusion), Tecartus (brexucabtagene autoleucel intravenous infusion) Yescarta (axicabtagene ciloleucel intravenous infusion), Abecma (idecabtagene vicleucel intravenous infusionion) and Carvykti (ciltacabtagene autoleucel intravenous infusion).

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.

SOURCES OF INFORMATION

1. Kymriah™ intravenous infusion [prescribing information]. East Hanover, NJ: Novartis Oncology; December 2024.
2. The NCCN Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (version 3.2024 – December 20, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 24, 2025.
3. The NCCN Drugs and Biologics Compendium. © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 24, 2025. Search term: tisagenlecleucel.
4. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 2.2025 – February 10, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 25, 2025.
5. The NCCN Pediatric Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (version 2.2025 – December 16, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 24, 2025.
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. Revision date: 10/2024. Accessed March 25, 2025.

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 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."	04/03/2020
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.	04/14/2021

	Conditions Not Recommended for Approval: Removed criterion for Retreatment with Kymriah (not needed since addressed in criteria section).	
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
Policy revision	**B-Cell Lymphoma:** Follicular was changed to indolent in the option for approval "diffuse large B-cell lymphoma arising from indolent lymphoma." Removed diffuse large B-cell lymphoma arising from nodal marginal zone lymphoma. Based on review of commercial policy revision	04/22/2024
Aspirus P&T Review	Policy reviewed and approved by Aspirus P&T committee. Annual review process	09/16/2024
Policy review	No criteria changes. Review based on NCD surveillance review.	01/06/2025
Policy revision	No criteria changes. Formatting and notation updates.	03/11/2025
Policy revision	**B-Cell Lymphoma:** Follicular lymphoma moved to an option for approval if the medication is used for relapsed or refractory disease after two or more lines of systemic therapy. Added Note with examples of systemic therapy. Large B-cell lymphoma, diffuse large B-cell lymphoma, diffuse large B-cell lymphoma arising from indolent lymphoma, high-grade B-cell lymphoma, human immunodeficiency virus (HIV)-related B-cell lymphoma, human herpes virus 8-positive diffuse large B-cell lymphoma, primary effusion lymphoma, post-transplant lymphoproliferative disease, B-cell type moved to new options for approval; if medication is used for disease that is relapsed or refractory after two or more lines of systemic therapy, or disease relapse > 12 months after first-line therapy and partial response to second-line therapy were added as options of approval. Added Notes with examples of systemic therapy. Added HIV-related plasmablastic lymphoma as a new option for approval. Revision based on commercial policy update	03/25/2025

Aspirus P&T Review	Policy reviewed and approved by Aspirus P&T committee. Annual review process	09/15/2025