CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL POLICY

Tisagenlecleucel (Kymriah®)

Version: 1.0

EFFECTIVE DATE: 1/1/2024

NantHealth® | Eviti®

Please note the following:

Tisagenlecleucel (Kymriah®)

Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Please refer to the CMS website at http://www.cms.gov for additional information.

Note: For Medicaid members/enrollees, circumstances when state Medicaid coverage provisions conflict with the coverage provisions within this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Tisagenlecleucel (Kymriah): Discussion

Tisagenlecleucel is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of:

- Patients less than or equal to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse; and
- 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; and
- Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy (accelerated approval). [1]

Tisagenlecleucel is made by collecting T cells from the patient and re-engineering them in the laboratory to produce proteins on their surface called chimeric antigen receptors, or CARs. The CARs recognize and bind to specific proteins, or antigens, on the surface of cancer cells. After the revamped T cells are "expanded" into millions in the laboratory, they are then infused back into the patient. The CAR T cells will continue to multiply in the patient's body and, with guidance from their engineered receptor, recognize and kill any cancer cells that harbor the target antigen on their surfaces. [2]

Acute lymphoblastic leukemia (ALL) is a heterogenous hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs. The median age at diagnosis of ALL is 15 years with 55.4% of patients diagnosed at younger than 20 years of age. In contrast, 28% of cases are diagnosed at ≥ 45 years and approximately 12.3% of patients are diagnosed at ≥65. ALL represents 75%-80% of acute leukemias among children, making it the most common form of childhood leukemia; by contrast, ALL represents 20% of all leukemias among young adults. [3,4]

Non-Hodgkin's lymphoma (NHL) is a heterogenous group of lymphoproliferative disorders originating in B-lymphocytes, T-lymphocytes, or natural killer (NK) cells (NK/T cell lymphomas are very rare). Diffuse large B-cell lymphomas (DLBCL) account for 32% and 17% respectively of all NHL's. Follicular lymphoma is the most common subtype of indolent NHL, and accounts for 22% of all newly diagnosed NHL. [5]

Due to the complications from CAR-T therapies of Cytokine Release Syndrome (CRS) as well as neurologic deficits, all providers/healthcare facilities involved in the treatment of patients getting CAR-T therapy, must be registered in the Tisagenlecleucel Risk Evaluation and Mitigation Strategy (REMS) Program. [6] In a single-arm phase II trial of 75 children and young adults with relapsed/refractory ALL, CRS occurred in 77% of patients, including 48% of patients with ≥ grade 3 CRS. The median time to onset and resolution was 3 and 8 days, respectively. In a second single-arm phase II study of 115 adults with relapsed/refractory (r/r) DLBCL, CRS occurred in 74% of patients, including ≥ Grade 3 CRS occurring in 23% of patients. The median times to onset and resolution of CRS were 3 days and 7 days, respectively. In the phase II Elara study, patients with relapsed/refractory FL, CRS occurred in 53% of patients (the majority were grade 1 and 2). The median time to onset and resolution for CRS was 4 days and 4 days, respectively. [1]

Neuro toxicity can occur in combination with CRS. For patients with r/r, ALL, neurological toxicities occurred in 71% of patients including ≥ Grade 3 in 22%. The median time to the first event and duration was 6 days and 7 days, respectively. Neurological toxicity for r/r DLBCL occurred in 60% of patients, including 19% with ≥ Grade 3. The median time to the first event and duration were 8 days and 5 days, respectively. For r/r follicular lymphoma, 43% of patients had neurologic toxicity, including 6% with ≥ Grade 3. The median time from the first event and duration were 8 days and 5 days, respectively. [1]

The NCCN endorses approval of tisagenlecleucel for the following indications:

a) DLBC
b) Follicular lymphoma
c) High-Grade B-Cell lymphoma
d) Histologic transformation of indolent lymphomas (follicular and nodal marginal zone lymphoma to DLBCL)
e) HIV-related B-cell lymphomas (includes primary effusion lymphoma, HIV-related DLBCL, and HHV8-positive DLBCL, not otherwise specified)
f) Post Transplant Lymphoproliferative Disorder
g) Acute Lymphoblastic Leukemia for patients under the age of 26. [3,4,5]

Tisagenlecleucel: Definitions

- **Cytokine release syndrome (CRS) -** A life-threatening complication of CAR-T therapy. Among patients with CRS, key manifestations include fever (93% in r/r ALL;85% in r/r DLBCL;92% in FL), hypotension (69% in r/r ALL; 45% in r/r DLBCL; 40% in r/r FL), hypoxia (57% in r/r ALL; 35% in r/r DLBCL; 19% in r/r FL) and tachycardia (26% in r/r ALL; 13% in r/r DLBCL;2% in r/r FL). [1]
- **Food and Drug Administration (FDA) -** The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.
- **Hemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS) –** A life-threatening condition has occurred with patients receiving

tisagenlecleucel. This occurred during ongoing CRS. Presenting symptoms are like those of CRS and infections. [1]

- **National Comprehensive Cancer Network (NCCN) -** An alliance of 32 leading cancer centers devoted to patient care, research, and education. The NCCN guidelines are utilized for Radiation Therapy and Medical Oncology standards. NCCN consensus clinical standards are periodically updated and NantHealth, Inc. reviews these and updates its policies within a timely manner.
- **Neurologic Toxicities -** Can be severe and life-threatening. The most common toxicities observed with tisagenlecleucel include headache (35% in r/r ALL; 21% in r/r DLBCL; 25% in r/r FL), encephalopathy (30% in r/r ALL; 16% in r/r DLBCL; 3% in FL), delirium (19% in r/r ALL; 5% in r/r DLBCL; 1% in FL), anxiety (16% in r/r ALL; 10% in r/r DLBCL; 2% in r/r FL), sleep disorders (11% in r/r ALL; 10% in r/r DLBCL; 6% in FL), dizziness (5% in r/r ALL; 12% in r/r DLBCL; 8% in r/r FL), tremors (8% in r/r ALL; 6% in r/r DLBCL; 3% in r/r FL) and peripheral neuropathy (4% in r/r ALL; 12% in r/r DLBCL; 7% in r/r FL). [1]
- **Risk Evaluation and Mitigation Strategy (REMS) -** A REMS program is a drug safety program to manage known or potential risk associated with a drug and is required by the US Food and Drug Administration (FDA) to ensure that the benefits of a drug outweigh its risks. Tisagenlecleucel is only available through this restricted program. The program ensures that hospitals and their associated clinic(s) that dispense tisagenlecleucel are specially certified and have on-site immediate access to tocilizumab. The program also ensures that those who prescribe, dispense, or administer tisagenlecleucel are aware of how to manage the risks of CRS and neurologic toxicities. Those involved in the program must successfully complete the knowledge assessment and submit it to the REMS Program. [6]
- **Relapsed or Refractory Disease (r/r) -** A term often used to describe treatment for lymphomas and leukemias. Relapsed disease is when cancer cells grow again after a remission period and refractory means that the disease is not responding to the treatment the patient is on.

Tisagenlecleucel: Policy

Tisagenlecleucel will be considered for coverage when the following criteria are met:

Acute Lymphoblastic Lymphoma:

For authorization:

1. 25 years of age or less; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Healthcare facility/provider has enrolled in the Tisagenlecleucel REMS Program; AND
4. Documentation of CD19 tumor expression; AND

5. Has a diagnosis of relapsed or refractory B-cell precursor Acute Lymphoblastic Leukemia; AND
6. The disease is refractory or in second or later relapse; AND
7. Therapy is given for one of the following indications in pediatrics:
   a) Ph-negative or Ph-like B-ALL that is minimal residual disease positive (MRD+) after consolidation therapy.
   b) Ph-positive B-ALL with less than complete response or MRD+ at the end of consolidation.
   c) Relapsed-refractory Ph-negative B-ALL that is refractory or ≥ 2 relapses.
   d) Relapsed/refractory Ph-positive TKI intolerant/refractory B-ALL or relapse post-HSCT; OR
8. Therapy is given for one of the following in adult patients ≤ 25 years of age with relapsed/refractory disease or ≥ 2 relapses:
   a) Philadelphia chromosome-positive B-ALL and failure of 2 TKI's
   b) Philadelphia chromosome-negative B-ALL; AND
9. A lymphodepleting chemotherapy of fludarabine and cyclophosphamide is given at the physician's discretion and tisagenlecleucel will be infused 2 to 14 days after completion of the lymphodepleting regimen.

Dosage:

Dosage/Quantity limit:

1. Patients 50 kg or less: administer 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg body weight.
2. Patients above 50 kg: administer 0.1-2.5 x 10^8 CAR-positive viable T cells.

Large B-Cell Lymphoma

For authorization:

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Healthcare facility/provider has enrolled in the Tisagenlecleucel REMS Program; AND
4. Diagnosis of relapsed or refractory large B-cell lymphoma including one of the following:
   a) Diffuse large B-cell lymphoma (DLBCL) not otherwise specified
   b) High-grade B-cell lymphoma.
   c) DLBCL arising from follicular lymphoma.
   d) HIV-related B-cell lymphoma. Must have appropriate supportive care measures for HIV control.
   e) Post-Transplant Lymphoproliferative Disorders (PTLD); AND
5. Third-line or subsequent therapy for DLBLC and HIV-related DLBCL, primary effusion lymphoma, and HHV8-positive DLBCL, not otherwise specified as:

a) Additional therapy for r/r disease > 12 months after completion of first-line therapy if partial response following second-line therapy
b) Treatment (if anti-CD19 CAR T-cell therapy was not previously given) of disease in second relapse or greater if partial response, no response, or progressive disease following therapy for r/r disease; OR

6. Third-line or subsequent therapy for r/r High-Grade B-cell lymphomas as:
   a) Additional therapy for r/r disease > 12 months after first-line therapy if the intention is to proceed to transplant if there is a partial response to second-line therapy
   b) Treatment (if anti-CD19 CAR T-cell therapy not previously given) of disease in second relapse or greater if partial response, no response, or progressive disease following therapy for relapsed or refractory disease; OR
7. Third-line and subsequent therapy (if anti-CD19 CAR T-cell therapy was not previously given) for histologic transformation to diffuse large B-cell lymphoma from follicular lymphoma or nodal marginal zone lymphoma after multiple lines of therapies including ≥ 2 chemoimmunotherapy regimens for indolent or transformed disease (treatment should have included at least one anthracycline or anthracenedione-based regimen, unless contraindicated); OR
8. Third-line and subsequent therapy for monomorphic PTLD (B-cell type) as for one of the following indications:
   a) Additional therapy for r/r disease > 12 months after completion of initial treatment with chemoimmunotherapy in patients who have partial response following second-line chemoimmunotherapy
   b) Treatment (if anti-CD19 CAR T-cell therapy not previously given) of disease in second relapse or greater in patients with partial response, no response, or progressive disease following therapy for r/r disease; AND
9. Pre-screening completed for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) prior to collection of cells (negative results must be submitted); AND
10. Eastern cooperative oncology group (ECOG) performance status of 0 or 1; AND
11. Does not have any of the following:
    a) Prior allogeneic HSCT
    b) Prior CAR-T therapy
    c) Active primary central nervous system lymphoma; AND
12. The individual will receive a lymphodepleting chemotherapy regimen once the tisagenlecleucel is ready. The regimen of cyclophosphamide and fludarabine OR bendamustine (if a patient experienced a grade 4 hemorrhagic cystitis with cyclophosphamide or demonstrates resistance to a previous cyclophosphamide-containing regimen) will be given at the physician's discretion. Infusion of tisagenlecleucel should be given 2-11 days after completion of the lymphodepleting chemotherapy; AND
13. If the white blood cell (WBC) count is less than 1 x 10^9/L within 1 week prior to tisagenlecleucel infusion.

Dosage:

Dosage/Quantity limit:

0.6 to 6.0 x 10^8 CAR-positive viable T-cells

Follicular Lymphoma

For Authorization:

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Healthcare facility/provider has enrolled in the Tisagenlecleucel REMS Program; AND
4. Third-line and subsequent therapy (if not previously given) for partial response, no response, or progressive disease in patients with indications for treatment; AND
5. Eastern cooperative oncology group (ECOG) performance status 0 or 1; AND
6. Does not have any of the following:
   a) Prior allogeneic HSCT
   b) Prior CAR-T therapy
   c) Active primary central nervous system lymphoma
   d) Follicular lymphoma grade 3B; AND
7. Pre-screening was completed for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) prior to the collection of cells. (Negative results must be submitted); AND
8. The individual will receive a lymphodepleting chemotherapy regimen once Kymriah is ready. The regimen of cyclophosphamide and fludarabine OR bendamustine (if a patient experienced a grade 4 hemorrhagic cystitis with cyclophosphamide or demonstrates resistance to a previous cyclophosphamide containing regimen) will be given at the physician's discretion. Infusion of tisagenlecleucel should be given 2-6 days after completion of the lymphodepleting chemotherapy; AND
9. If the white blood cell (WBC) count is less than 1 x 10^9/L within 1 week prior to tisagenlecleucel infusion

Dosage:

Dosage/Quantity limit:

0.6 to 6.0 x 10^8 CAR-positive viable T-cells.

For reauthorization:

Tisagenlecleucel is a one-time dose and will not be renewed.

Note: Coverage of tisagenlecleucel will be provided for FDA-approved indications or National Comprehensive Cancer Network (NCCN) guidelines when it is a Category 1, 2A, or 2B recommendation or when all criteria are met.

Tisagenlecleucel: References

1. Tisagenlecleucel (Kymriah) Package Insert. https://www.fda.gov/media/107296/download. Accessed May 23, 2023.
2. CAR T Cells: Engineering Patients' Immune Cells to Treat Their Cancers. https://www.cancer.gov/about-cancer/treatment/research/car-t-cells/. Accessed May 23, 2023.
3. National Comprehensive Cancer Network. Acute Lymphoblastic Leukemia (Version 1.2022). http://www.nccn.org/professionals/physician_gls/pdf/all.pdf. Accessed May 23, 2023.
4. National Comprehensive Cancer Network. Pediatric Acute Lymphoblastic Leukemia (Version 2.2023). www.nccn.org/professionals/physician_gls/pdf/ped_all.pdf. Accessed May 23, 2023.
5. National Comprehensive Cancer Network. B-Cell Lymphomas (Version 3.2023). http://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed May 23, 2023.
6. Kymriah REMS program. https://www.kymriah-rems.com/. Accessed May 24, 2023.
7. Buechner et al, Eur Hematol Assoc: Oral Presentation S476;2017. https://learningcenter.ehaweb.org/eha/2017/22nd/181763/stephan.a.grupp.global.registration.trial.of.efficacy.and.safety.of.ctl019.in.html?f=m3l15672. Accessed May 26, 2023.
8. Schuster et al, N Engl J Med 380:45-56;2019. https://www.ncbi.nlm.nih.gov/pubmed/30501490 Accessed May 26. Accessed May 26, 2023.
9. Thieblemont et al, Blood 138: A131-35;2021. https://www.sciencedirect.com/science/article/pii/S0006497121021285#ceab10. Accessed May 26, 2023.

Tisagenlecleucel: Coding (CPT®, ICD 10 and HCPCS) *

*Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all-inclusive and is subject to updates. In addition, the codes listed are not a guarantee of payment. CPT codes are available through the AMA.

CODE	DESCRIPTION
Q2042	Tisagenlecleucel, up to 600 million car-positive viable T cells, including leukapheresis and dose preparation procedures, per therapeutic dose
C91.00	Acute lymphoblastic leukemia not having achieved remission
C91.02	Acute lymphoblastic leukemia, in relapse
C83.30-C83.39	Diffuse large B-cell coding

C82.00-C82.09	Follicular lymphoma grade I
C82.10-C82.19	Follicular lymphoma grade II
C82.20-C82.29	Follicular lymphoma grade III, unspecified
C82.30-C82.39	Follicular lymphoma grade IIIa
C82.40-C82.49	Follicular lymphoma grade IIIb
C82.50-C82-59	Diffuse follicle center lymphoma
C82.60-C82.69	Cutaneous follicle center lymphoma
C82.80-C82-89	Other types of follicular lymphoma
C82.90-C82.99	Follicular lymphoma, unspecified
Z51.12	Encounter for antineoplastic immunotherapy
XW033C3	Introduction of engineered autologous chimeric antigen receptor T cell immunotherapy into peripheral vein, percutaneous approach, new technology group
XW043C3	Introduction of engineered autologous chimeric antigen receptor T cell immunotherapy into central vein, percutaneous approach, new technology group
0537T	Chimeric antigen receptor T cell (CAR-T) therapy; harvesting of blood-derived T lymphocytes for development of genetically modified autologous CAR-T cells, per day
0538T	Chimeric antigen receptor T cell (CAR-T) therapy; preparation of blood-derived T lymphocytes for transportation (e.g., cryopreservation, storage)
0539T	Chimeric antigen receptor T cell (CAR-T) therapy; receipt and preparation of CAR-T cells for administration
0540T	Chimeric antigen receptor T cell (CAR-T) therapy; CAR-T cell administration, autologous
0871	Cell/Gene Therapy – Cell Collection bill with 0537T
0872	Cell/Gene Therapy – Specialized Biologic Processing and Storage - Prior to Transport-bill with 0538T
0873	Cell/Gene Therapy – Storage and Processing after Receipt of Cells from Manufacturer-bill with 0539T
0874	Cell/Gene Therapy – Infusion of Modified Cells-bill with 0540T
0875	Cell/Gene Therapy – Injection of Modified Cells-bill with 0540T

0891	Special Processed Drugs – FDA-Approved Cell Therapy-bill with Q2042

Tisagenlecleucel: Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	1/1/2024
2	Policy Review Dates:	6/6/2023
3	Policy Revision Dates:	
4	Department Owner:	Medical Affairs
5	NH Advisory Committee Approval Dates:	6/20/2023
6	Revision Changes:	