Oscar Clinical Guideline: Kymriah (tisagenlecleucel) (CG058, Ver. 7)

Kymriah (tisagenlecleucel)

Summary

The Plan members who have certain types of treatment-resistant lymphoma or leukemia may be eligible for chimeric antigen receptor (CAR) T-cell therapy. CAR T-cell treatment involves genetically modifying a patient's white blood cells to specifically target the cancer cells in the body. This type of therapy is also known as adoptive immunotherapy. The process involves:

1. Collecting a patient's white blood cells (T-cells) from their blood.
2. Genetically modifying the T-cells in a lab to express CARs that target specific cancer cell antigens (like CD19).
3. Multiplying the number of these CAR T-cells.
4. Depleting the patient's existing immune system, often with chemotherapy.
5. Infusing the expanded CAR T-cells back into the patient.

   The modified CAR T-cells can then recognize and attack cancer cells expressing the targeted antigen. They may continue to multiply and remain in the body long-term, potentially guarding against cancer recurrence .

CAR T-cell therapy should only be performed when benefits outweigh risks, under the care of a licensed physician at a certified treatment facility.

- Kymriah can only be accessed at specific treatment centers. To obtain more information, contact the REMS Call Center at 1-844-4KYMRIAH (1-844-459-6742) or visit https://www.kymriah-rems.com/.
    - The facility must be able to provide:
        - Adequate inpatient monitoring during infusion.
        - At least two doses of tocilizumab on hand for severe adverse reactions.
        - Close outpatient monitoring with transplant/CAR T-cell experience.
- Patients receiving these treatments should be monitored life-long for new malignancies.
    - Patients need to remain near the treatment facility for monitoring for at least 4 weeks post-treatment.
    - The FDA has received reports of T-cell malignancies[29], including CAR-positive lymphoma, in patients treated with BCMA-directed or CD19-directed autologous CAR T-cell therapies . While overall benefits still outweigh risks for approved uses, the FDA is investigating this serious risk, which has led to hospitalizations and deaths, and evaluating the need for regulatory action.

This guideline does not address adoptive T-cell therapy for metastatic prostate cancer: Sipuleucel-T (Provenge™). For sipuleucel-T (Provenge™), please review the criteria outlined in MCG Sipuleucel-T (A-0661).

Definitions:

"Allogeneic Stem Cell Transplant" is a treatment where donor stem cells are harvested and transferred into patients with cancer or disorders (after their own immune system has been depleted using chemotherapy or total body irradiation) to repopulate their entire bone marrow with healthy cells.

"Autologous Stem Cell Transplant" is similar to allogeneic stem cell transfer, except the patient's own stem cells are used instead of a matched donor.

"B-cell lymphomas" refer to a group of non-Hodgkin's lymphomas developing from cancerous white blood cells (specifically B-lymphocytes), often involving lymph nodes or other extranodal tissues. This group of lymphomas includes, but is not limited to, the following:

- Burkitt lymphoma
- Diffuse large B-cell lymphoma (DLBCL)

- Primary mediastinal B-cell lymphoma (PMBCL)
- Mantle cell lymphoma
- Marginal zone lymphomas
- Transformed follicular lymphoma

"CAR T-cell" or "Chimeric Antigen Receptor T-cell" therapy is a type of adoptive immunotherapy where a patient's white blood cells (specifically T-lymphocytes) are genetically engineered to specifically target the receptors on the cancer cells (CD19 receptor in the case of B-cell lymphomas and leukemias), B-cell maturation antigen (BCMA) or prostatic acid phosphatase (PAP) in the case of prostate cancer).

"**CAR-T cell-related encephalopathy syndrome" (CRES)** is another inflammatory immune response that can occur with CAR-T treatment and is treated in the same way as CRS.

"**Cytokine release syndrome" (CRS)** is an inflammatory immune response that may occur with CAR T-cell treatment. It often manifests as fever, hypotension, nausea, and other symptoms, and is an emergent condition that may require prompt treatment with tocilizumab (treatment binds to and inhibits IL-6 to reduce inflammatory and immune excessive response) and/or corticosteroids.

"**ECOG score" (**Eastern Cooperative Oncology Group) is a measure of a patient's general well-being and ability to participate in activities of daily living. The score ranges from 0 (fully active with restrictions) to 5 (dead) and is available at https://ecog-acrin.org/resources/ecog-performance-status.

"Leukemia" refers to a type of malignancy affecting the bone marrow and circulating cells in the bloodstream. Acute lymphoid leukemia (ALL) is one example.

"**Metastatic Castrate-Resistant Prostate Cancer"** is prostate cancer that has metastasized or spread outside of the pelvis. Castrate-resistant refers to the state of the cancer not responding to medications or systemic agents that typically inhibit progression by blocking hormonal signals.

"Relapsed" refers to a lymphoma or leukemia that had previously responded to treatment with remission, but has returned after a period since the last treatment.

"Refractory" refers to a lymphoma or leukemia that has not responded, has progressed, or has not achieved remission.

Medical Necessity Criteria for Authorization

The Plan considers **Kymriah (tisagenlecleucel)** medically necessary when **ALL** the following criteria are met:

1. Prescribed by or in consultation with a hematologist-oncologist**; *AND***
2. Documented evidence of **ALL** of the following:
    a. The member is scheduled for and can safely undergo lymphodepleting therapy (including chemotherapy and/or total body irradiation) before CAR T-cell treatment**; *and***
    b. The healthcare facility administering Kymriah is enrolled and adheres to the Kymriah REMS (Risk Evaluation and Mitigation Strategy), which includes:
        i. Immediate, on-site availability of tocilizumab**; *and***
        ii. Provision of a minimum of two tocilizumab doses per patient, ensuring administration within 2 hours after Kymriah infusion if required for cytokine release syndrome treatment**; *and***
        iii. Healthcare providers involved in prescribing, dispensing, or administering Kymriah are trained in managing cytokine release syndrome and neurological side effects**; *and***
    c. The member has undergone screening and does **NOT** have any of the following:
        i. Active Central Nervous System (CNS) involvement by malignancy**; *or***
        ii. Active uncontrolled infection or inflammatory disorders**; *or***
        iii. Active or latent hepatitis B**; *or***
        iv. Active hepatitis C**; *or***

            NOTE: history of hepatitis B or C is acceptable if the viral load is currently non-detectable.

        v. A positive Human Immunodeficiency Virus (HIV) test**; *or***
        vi. In patients with a history of allogeneic stem cell transplantation, active graft vs. host disease (GVHD)**; *or***
        vii. Previous treatment with Kymriah or any other CD19-targeted CAR T-cell therapy**; *AND***
3. No contraindications (listed in "**Experimental or Investigational / Not Medically Necessary**" exclusions) are present**; *AND***
4. The member meets the medical necessity criteria for the applicable indication listed below:

Acute lymphoblastic leukemia, relapsed or refractory

The Plan considers **Kymriah (tisagenlecleucel)** medically necessary when the member has documented evidence of **BOTH** of the following:

1. B-cell precursor acute lymphoblastic leukemia (ALL)**; *AND***
2. Characterized by **ONE** of the following:
    a. Is less than 18 years of age **AND** has documented evidence of **ONE** of the following:
        i. Philadelphia chromosome-negative B-ALL that is refractory or in second or later relapse (≥ 2 relapses)**; *or***
        ii. Philadelphia (Ph) chromosome-negative or Ph-like B-ALL that is minimal residual disease positive (MRD+) after consolidation therapy**; *or***
        iii. Philadelphia chromosome-positive B-ALL **AND ONE** of the following:
            1. Refractory to at least **TWO** tyrosine kinase inhibitors (e.g., bosutinib, dasatinib, imatinib, nilotinib, ponatinib), unless contraindicated/intolerant**; *or***
            2. Relapse post-hematopoietic stem cell transplant (HSCT)**; *or***
            3. With less than complete response or MRD+ at end of consolidation therapy**; *or***
    b. Is 18 to 25 years of age **with** B-ALL that is refractory or in second or later relapse (≥ 2 relapses) **AND** documented evidence of **ONE** of the following:
        i. Philadelphia chromosome-negative B-ALL**; *or***
        ii. Philadelphia chromosome-positive B-ALL **AND** and failure of 2 tyrosine kinase inhibitors (e.g., bosutinib, dasatinib, imatinib, nilotinib, ponatinib), unless contraindicated/intolerant**.**

B-Cell Lymphomas

B-cell Lymphomas, relapsed or refractory

The Plan considers **Kymriah (tisagenlecleucel)** medically necessary when the member has documented evidence of **ALL** of the following:

1. The member is 18 years of age or older**; *AND***
2. **ONE** of the following relapsed or refractory large B-cell lymphoma:
    a. AIDS-related B-cell lymphoma**; *or***
    b. Diffuse large B-cell lymphoma**; *or***
    c. HHV-8 associated B-cell lymphoma**; *or***
    d. Monomorphic post-transplant lymphoproliferative disorder (B-cell type)**; *or***
    e. Other high-grade B-cell lymphoma**; *or***

f. Transformed follicular lymphoma (into an aggressive large B-cell lymphoma)**; *or***
g. Transformed nodal marginal zone lymphoma (into diffuse large B-cell lymphoma)**; *AND***

3. The member has received prior treatment with at least **TWO** prior lines of systemic therapy.
    a. For members with CD20-positive tumors, previous chemoimmunotherapy regimens must have included an anti-CD20 monoclonal antibody (e.g., Rituxan or rituximab biosimilars), unless contraindicated**; *and***
    b. For diffuse large B-cell lymphoma arising from follicular lymphoma **OR** nodal marginal zone lymphoma - documented evidence of **BOTH** of the following:
        i. The two lines of therapy have been given **after** malignant transformation**; *or***
        ii. chemoimmunotherapy regimens included at least one anthracycline or anthracenedione-based regimen, unless contraindicated**.**

Follicular lymphoma, relapsed or refractory

The Plan considers **Kymriah (tisagenlecleucel)** medically necessary when the member has documented evidence of **BOTH** of the following:

1. The member is 18 years of age or older**; *AND***
2. Follicular lymphoma characterized by **ONE** of the following:
    a. Refractory to a second line or later line of systemic therapy (including an anti-CD20 antibody and an alkylating agent)**; *or***
    b. Relapsed within 6 months after completion of a second line or later line of systemic therapy**; *or***
    c. Relapsed during or within six months after completion of an anti-CD20 antibody maintenance therapy following at least two lines of therapy**; *or***
    d. Relapsed after autologous hematopoietic stem cell transplant (HSCT)**.**

Length of Stay

Initial Inpatient Admission - Up to 7 days

Extension Stay Criteria

Additional inpatient hospital days after 7 days are medically necessary when:

1. Patient has cytokine release syndrome (CRS)**; *OR***
2. Patient has neurotoxicity, CAR-T Related Encephalopathy Syndrome (CRES)**; *OR***
3. Patient has developed any adverse reaction continuing after infusion that include, but are not limited to, fever, hypoxia, hypotension, tachycardia, hypersensitive reactions,

hypogammaglobulinemia, infections-pathogen unspecified, bleeding episodes, diarrhea, nausea, vomiting, headache, acute kidney injury, edema, and delirium**; *OR***

4. Patient is not stable for discharge, as outlined in the general recovery course and discharge criteria in MCG General Recovery Care > Problem Oriented General Recovery Guidelines >Medical Oncology GRG (PG-ONC).

Experimental or Investigational / Not Medically Necessary

CAR T-cell therapy for any other indication is considered experimental, investigational, or unproven. Non-covered indications and contraindications include, but are not limited to, the following:

- Any lymphoma subtype not mentioned above, including primary CNS lymphoma and Mantle cell lymphoma**; *OR***
- Any leukemia subtype except acute lymphoid leukemia (ALL)**; *OR***
- Any other cancer type or condition not included in the Clinical Indications criteria above**; *OR***
- Burkitt's lymphoma/leukemia (i.e. patients with mature B-cell ALL, leukemia with B-cell [sIg positive and kappa or lambda restricted positivity] ALL, with FAB L3 morphology and/or a MYC translocation)**; *OR***
- When any other newly diagnosed malignancy or other malignancy that is under active treatment or not currently in remission is present**; *OR***
- Patients with an ECOG score of 3-4, as the efficacy and evidence for use in patients with poor performance status is limited**; *OR***
- Any of the following contraindications:
    - Active HIV**; *or***
    - Active, severe systemic infection including but not limited to those currently requiring IV antibiotics**; *or***
    - Current pregnancy**; *or***
    - Hepatitis B or Hepatitis C with detectable viral load**; *or***
    - Live vaccination within 6 weeks of planned treatment date**; *or***
    - Uncontrolled central nervous system disease, including but not limited to brain metastases, positive CSF disease, seizure disorder, dementia, history of stroke, cerebellar disease, or autoimmune CNS disease.

Applicable Billing Codes (HCPCS/CPT Codes)

CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
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 (eg, 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
96365 - 96368	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug)
96413 - 96417	Chemotherapy administration, intravenous infusion technique
Q2042	Tisagenlecleucel, up to 600 million CAR-positive viable T cells, including leukapheresis and dose preparation procedures, per therapeutic dose
ICD-10 codes considered medically necessary if criteria are met for Tisagenlecleucel (Kymriah™):	
Code	*Description*
B20	Human immunodeficiency virus [HIV] disease
C82.00 - C82.99	Follicular lymphoma
C83.00 - C83.09	Small cell B-cell lymphoma
C83.30 - C83.39	Diffuse large B-cell lymphoma
C83.50-C83.59	Lymphoblastic (diffuse) lymphoma
C83.80-C83.89	Other non-follicular lymphoma
C83.90-C83.99	Non-follicular (diffuse) lymphoma, unspecified
C85.10 - C85.19	Unspecified B-cell lymphoma
C85.20-C85.29	Mediastinal (thymic) large B-cell lymphoma
C85.80 - C85.89	Other specified types of non-Hodgkin lymphoma

C91.00 - C91.02	Acute lymphoblastic leukemia
D47.Z1	Post-transplant lymphoproliferative disorder (PTLD)
Z85.72	Personal history of non-Hodgkin lymphomas
ICD-10 codes considered experimental of investigational for Tisagenlecleucel (Kymriah™) ***NOTE: This list of codes may not be all-inclusive.***	
C71.0 - C71.9	Malignant neoplasm of the brain
C74.00 - C74.92	Malignant neoplasm of adrenal gland
C81.00 - C81.99	Hodgkin lymphoma
C83.10 - C83.19	Mantle cell lymphoma
C83.70- C83.79	Burkitt lymphoma
C84.A0 - C84.A9	Cutaneous T- lymphoma, unspecified
C84.60 - C84.79	Anaplastic large cell lymphoma, ALK- or negative
C90.00 - C90.02	Multiple myeloma
C90.20 - C90.22	Extramedullary plasmacytoma
C91.10 - C91.12	Chronic lymphocytic leukemia (CLL)
C91.50 - C91.52	Adult T-cell leukemia/lymphoma (HTLV-1 associated)
C91.60 - C91.62	Prolymphocytic leukemia of T-cell type
C92.00 - C92.02	Acute myeloblastic leukemia

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