Clinical Policy: Tisagenlecleucel (Kymriah)

Reference Number: PA.CP.PHAR.361
Effective Date: 09.26.2017
Last Review Date: 01.2023

Revision Log

Description
Tisagenlecleucel (Kymriah™) is a CD19-directed, genetically modified, autologous T-cell immunotherapy.

FDA Approved Indication(s)
Kymriah 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
- Adult patients with relapsed or refractory large B-cell lymphoma (LBCL) 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
- Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy^

Limitation(s) of use: Kymriah is not indicated for treatment of patients with primary central nervous system lymphoma.*

**Efficacy of Kymriah for the treatment of LBCL has not been established in patients with active CNS disease (see Appendix D)*
^ 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 trials.

Policy/Criteria
Provider must submit documentation (which may include office chart notes and lab results) supporting that member has met all approval criteria

It is the policy of PA Health & Wellness that Kymriah **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Acute Lymphoblastic Leukemia (must meet all)**:**

1. Diagnosis of B-cell precursor ALL;
2. Age ≤ 25;
3. Prescribed by or in consultation with an oncologist or hematologist;
4. Documentation of CD19 tumor expression;
5. Recent (within the last 30 days) documentation of one of the following (a or b):
   a. Absolute lymphocyte count (ALC) ≥ 500/µL;
   b. CD3 (T-cells) cell count of ≥ 150/µL if ALC < 500/µL;

6. Request meets one of the following (a-f):
   a. Disease is refractory, defined as failure to achieve a complete response following induction therapy with ≥ 2 cycles of standard chemotherapy regimen (primary refractory) or after 1 cycle of standard chemotherapy for relapsed leukemia (chemorefractory);
   b. Member has had ≥ 2 relapses;
   c. Disease is Philadelphia chromosome positive (Ph+): Failure of 2 lines of chemotherapy that included 2 tyrosine kinase inhibitors (e.g., imatinib, Sprycel®, Tasigna®, Bosulif®, Iclusig®) at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated;
   **Prior authorization may be required for tyrosine kinase inhibitors*
   d. Disease is Philadelphia chromosome negative (Ph-) or Ph-like B-ALL that is minimal residual disease positive (MRD+) after consolidation therapy;
   e. Disease is Philadelphia chromosome positive (Ph+) with less than complete response or MRD+ at the end of consolidation;
   f. Member has relapsed following allogeneic stem cell transplantation (SCT) and must be ≥ 6 months from SCT at the time of Kymriah infusion;
7. Member has not previously received treatment with CAR T-cell immunotherapy (e.g., Abecma®, Breyanzi™, Tecartus®, Yescarta™);
8. Kymriah is not prescribed concurrently with other CAR T-cell immunotherapy (e.g., Abecma, Breyanzi, Tecartus, Yescarta);
9. Dose does not exceed (a or b):
   a. Weight ≤ 50 kg: 5.0×10^6 chimeric antigen receptor (CAR)-positive viable T cells per kg of body weight;
   b. Weight > 50 kg: 2.5×10^8 CAR-positive viable T cells.

Approval duration: 3 months ***(1 dose only, with 4 doses of tocilizumab (Actemra) at up to 800 mg per dose)***

B. Large B-Cell Lymphoma (must meet all)**:**
1. Diagnosis of one of the following LBCL (a-h):
   a. DLBCL;
   b. Primary Mediastinal Large B Cell Lymphoma (PMBCL);
   c. Transformed Follicular Lymphoma (TFL) to DLBCL;
   d. Transformed Nodal Marginal Zone lymphoma (MZL) to DLBCL;
   e. High-grade B-cell lymphomas with translocations of MYC and BCL2 and/or BCL6 (double/triple hit lymphoma) or high-grade B-cell lymphomas, not otherwise specified;
   f. Monomorphic post-transplant lymphoproliferative disorders (B-cell type);
   g. AIDS-related DLBCL, primary effusion lymphoma, and HHV8-positive DLBCL;
   h. Follicular Lymphoma grade 1-2
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Recent (within the last 30 days) ALC ≥ 300/µL;
5. Disease is refractory or member has relapsed after ≥ 2 lines of systemic therapy that includes rituximab and one anthracycline-containing regimen (e.g., doxorubicin);

**Prior authorization may be required for rituximab*

6. Member does not have active or primary CNS disease (*see Appendix D*);
7. Member has not previously received treatment with CAR T-cell immunotherapy (e.g., Abecma, Breyanzi, Tecartus, Yescarta);
8. Kymriah is not prescribed concurrently with other CAR T-cell immunotherapy (e.g., Abecma, Breyanzi, Tecartus, Yescarta);
9. Dose does not exceed 6.0 x 10^8 CAR-positive viable T cells.

Approval duration: 3 months ***(1 dose only, with 4 doses of tocilizumab (Actemra) at up to 800 mg per dose)***

C. Follicular Lymphoma* (must meet all)**:**

**Only for initial treatment dose; subsequent doses will not be covered.*

1. Diagnosis of FL grade 1, 2, or 3a;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Request meets one of the following (a or b):
   a. Disease is relapsed/refractory after ≥ 2 lines of systemic therapy that includes a combination of an anti-CD20 monoclonal antibody (e.g., rituximab or Gazyva®) and an alkylating agent (e.g., bendamustine, cyclophosphamide, chlorambucil)*;
      **Prior authorization may be required*
   b. Member has relapsed following autologous SCT;
5. Member does not have active CNS involvement by malignancy;
6. Member has not previously received treatment with CAR T-cell immunotherapy (e.g., Abecma, Breyanzi, Tecartus, Yescarta);
7. Kymriah is not prescribed concurrently with other CAR T-cell immunotherapy (e.g., Abecma, Breyanzi, Tecartus, Yescarta);
8. Dose does not exceed a single administration of 6 x 10^8 CAR-positive viable T cells.

Approval duration: 3 months ***(1 dose only, with 4 doses of tocilizumab (Actemra) if requested at up to 800 mg per dose)***

D. Other diagnoses/indications

1. Refer to PA.CP.PMN.53 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. All Indications in Section I

Continued therapy will not be authorized as Kymriah is indicated to be dosed one time only.

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Refer to PA.CP.PMN.53 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policy – PA.CP.PMN.53 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ALC: absolute lymphocyte count
ALL: acute lymphoblastic leukemia
CAR: chimeric antigen receptor
CML: chronic myelogenous leukemia
CNS: central nervous system
CRS: cytokine release syndrome
CSF: cerebral spinal fluid
DLBCL: diffuse large B-cell lymphoma
FDA: Food and Drug Administration
FL: follicular lymphoma
LBCL: large B-cell lymphoma
MZL: marginal zone lymphoma
Ph+: Philadelphia chromosome positive
PMBCL: primary mediastinal large B-cell lymphoma
r/r: relapsed or refractory
REMS: risk evaluation and mitigation strategy
SCT: stem cell transplantation
TFL: transformed follicular lymphoma
WBC: white blood cell

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Acute Lymphoblastic Leukemia		
imatinib mesylate (Gleevec®)	Adults with Ph+ ALL: 600 mg/day Pediatrics with Ph+ ALL: 340 mg/m^2/day	Adults: 800 mg/day Pediatrics: 600 mg/day
Sprycel® (dasatinib)	Ph+ ALL: 140 mg per day	180 mg/day
Iclusig® (ponatinib)	Ph+ ALL: 45 mg per day	45 mg/day
Tasigna® (nilotinib)	Resistant or intolerant Ph+ CML-CP and CML-AP: 400 mg twice per day	800 mg/day
Bosulif® (bosutinib)	Ph+ CML: 500 mg per day	600 mg/day
Various combination regimens that may include the following: daunorubicin, doxorubicin, vincristine, dexamethasone, prednisone, pegaspargase, nelarabine, methotrexate, cyclophosphamide, cytarabine, rituximab, 6-mercaptopurine	Ph- ALL: varies	Varies
Large B-Cell Lymphoma		
First-Line Treatment Regimens		
RCHOP (Rituxan® (rituximab), cyclophosphamide, doxorubicin, vincristine, prednisone)	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
RCEPP (Rituxan® (rituximab), cyclophosphamide, etoposide, prednisone, procarbazine)	Varies	Varies
RCDOP (Rituxan® (rituximab), cyclophosphamide, liposomal doxorubicin, vincristine, prednisone)	Varies	Varies
DA-EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicine) + Rituxan® (rituximab)	Varies	Varies
RCEOP (Rituxan (rituximab), cyclophosphamide, etoposide, vincristine, prednisone)	Varies	Varies
RGCVP (Rituxan® (rituximab), gemcitabine, cyclophosphamide, vincristine, prednisone)	Varies	Varies
Second-Line Treatment Regimens		
Bendeka® (bendamustine) ± Rituxan® (rituximab)	Varies	Varies
CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) ± Rituxan® (rituximab)	Varies	Varies
CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± Rituxan® (rituximab)	Varies	Varies
DA-EPOCH ± Rituxan® (rituximab)	Varies	Varies
GDP (gemcitabine, dexamethasone, cisplatin) ± Rituxan® (rituximab)	Varies	Varies
gemcitabine, dexamethasone, carboplatin ± Rituxan® (rituximab)	Varies	Varies
GemOx (gemcitabine, oxaliplatin) ± Rituxan® (rituximab)	Varies	Varies
gemcitabine, vinorelbine ± Rituxan® (rituximab)	Varies	Varies
lenalidomide ± Rituxan® (rituximab)	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Rituxan (rituximab)	Varies	Varies
DHAP (dexamethasone, cisplatin, cytarabine) ± Rituxan® (rituximab)	Varies	Varies
DHAX (dexamethasone, cytarabine, oxaliplatin) ± Rituxan® (rituximab)	Varies	Varies
ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± Rituxan® (rituximab)	Varies	Varies
ICE (ifosfamide, carboplatin, etoposide) ± Rituxan® (rituximab)	Varies	Varies
MINE (mesna, ifosfamide, mitoxantrone, etoposide) ± Rituxan® (rituximab)	Varies	Varies
FL First-Line and Second-Line + Subsequent Treatment Regimens		
bendamustine + (Gazyva® (obinutuzumab) or rituximab)	Varies	Varies
CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + (Gazyva® (obinutuzumab) or rituximab)	Varies	Varies
CHOP + Gazyva® (obinutuzumab) or rituximab	Varies	Varies
CVP (cyclophosphamide, vincristine, prednisone) + Gazyva® (obinutuzumab)		
CVP + Gazyva® (obinutuzumab) or rituximab	Varies	Varies
rituximab ± (lenalidomide, chlorambucil, or cyclophosphamide)	Varies	Varies
rituximab	Varies	Varies
Gazyva® (obinutuzumab)	Varies	Varies
Zevalin® (ibritumomab tiuxetan)	Varies	Varies

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): none reported
- Boxed warning(s): cytokine release syndrome (CRS), neurological toxicities

Appendix D: General Information

- Refractory ALL is defined as complete remission not achieved after 2 cycles of standard chemotherapy or 1 cycle of standard chemotherapy due to relapsed leukemia.[2]
- CRS, including fatal or life-threatening reactions, occurred in patients receiving Kymriah. Do not administer Kymriah to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.
- Neurological toxicities, which may be severe or life-threatening, can occur following treatment with Kymriah, including concurrently with CRS. Monitor for neurological events after treatment with Kymriah. Provide supportive care as needed.
- Kymriah is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Kymriah REMS.
- Novartis, the manufacturer of Kymriah, recommends that patients with ALL have an ALC ≥ 500/µL for leukapheresis collection. Patients with an ALC < 500/µL during leukapheresis screening should have had a CD3 (T-cells) cell count of ≥ 150/µL to be eligible for leukapheresis collection.
- The JULIET trial in patients with DLBCL excluded patients with an ALC <300/µL.
- Patients with active CNS disease were excluded in the ELIANA trial for ALL and the JULIET trial for DLBCL. In the ALL trial, active CNS involvement by malignancy was defined by CNS-3 per NCCN guidelines (WBC ≥ 5/mcL in CSF with presence of lymphoblasts). In the DLBCL trial, active CNS involvement was assessed during screening by CNS symptom assessment to evaluate clinical evidence of CNS disease, CNS brain imaging (MRI/CT) if clinically indicated, and CSF cytology only if there was suspicion of CNS involvement.
- NCCN treatment guidelines for ALL state that CNS-directed therapy may include cranial irradiation, intrathecal chemotherapy (e.g., methotrexate, cytarabine, corticosteroids), and/or systemic chemotherapy (e.g., high-dose methotrexate, intermediate or high-dose cytarabine, pegaspargase). For primary DLBCL of the CNS (i.e., primary CNS lymphoma), NCCN treatment guidelines for CNS cancers recommend a high-dose methotrexate induction based regimen or other systemic therapy regimen if patient is unsuitable for or intolerant to high-dose methotrexate. If a complete response is achieved, or complete response unconfirmed, continue with consolidation therapy with high-dose chemotherapy with stem cell rescue, high-dose cytarabine with or without etoposide, low dose whole brain radiation therapy, or continuation with monthly high-dose methotrexate-based regimen. Alternatively, whole brain radiation therapy is recommended if patient is not a candidate for systemic chemotherapy.
- NCCN Pediatric ALL Version 1.2022 treatment guidelines state that Kymriah can be used in relapsed disease that includes medullary and/or extramedullary disease as CAR-T cells have shown activity against extramedullary disease. NCCN defines extramedullary as disease involving the CNS or testes.
- Frigault et al. 2019 reported on their institutional experience with 8 secondary CNS lymphoma patients treated with Kymriah. The best response assessed 28 days post-Kymriah infusion in these patients included complete responses (n = 2) and partial response (n = 2). Additionally, two patients died within 30 days of Kymriah infusion, the remaining two patients experienced disease progression. All patients were receiving CNS-directed therapy for refractory disease up until lymphodepletion.

- Enrollment in the JULIET trial in patients with DLBCL did not require CD19 positive tumor expression. In a subgroup analysis the best overall response rate was comparable between patients with unequivocal CD19 expression (49%, 95% CI 34 to 64, n = 49) and patients with low or negative CD19 expression (50%, 95% CI 29 to 71, n = 24).

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
ALL	≤ 50 kg: 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg of body weight IV > 50 kg: 0.1 to 2.5 x 10^8 CAR-positive viable T cells IV	≤ 50 kg: 5.0 x 10^6 CAR-positive viable T cells per kg of body weight > 50 kg: 2.5 x 10^8 CAR-positive viable T cells
LBCL	0.6 to 6.0 x 10^8 CAR-positive viable T cells IV	6.0 x 10^8 CAR-positive viable T-cells
FL	0.6 to 6.0 x 10^8 CAR-positive viable T cells IV	6.0 x 10^8 CAR-positive viable T-cells

**Kymriah should be administered at a certified healthcare facility*

VI. Product Availability

Single-dose unit infusion bag: frozen suspension of genetically modified autologous T cells labeled for the specific recipient

VII. References

1. Kymriah Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; August 2021. Available at: https://www.us.kymriah.com/. Accessed September 20, 2022.
2. Data on File. Novartis Pharmaceuticals Corporation; East Hanover, NJ. November 2020.
3. National Comprehensive Cancer Network. Acute Lymphoblastic Leukemia Version 2.2021. Available at https://www.nccn.org/professionals/physician_gls/pdf/all.pdf. Accessed September 20, 2022.
4. National Comprehensive Cancer Network. Pediatric Acute Lymphoblastic Leukemia Version 1.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/ped_all.pdf. Accessed September 20, 2022.
5. National Comprehensive Cancer Network Drug and Biologics Compendium. Available at http://www.nccn.org/professionals/drug_compendium. Accessed September 20, 2022.
6. National Comprehensive Cancer Network. B-Cell Lymphomas Version 4.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed September 20, 2022.
7. National Comprehensive Cancer Network. Central Nervous System Cancers Version 2.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed September 20, 2022.
8. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractor difuse large B-cell lymphoma. N Engl J Med 2019; 380(1): 45-56.
9. Frigault MJ, Dietrich J, Martinez-Lage M, et al. Tisagenlecleucel CAR T-cell therapy in secondary CNS lymphoma. Blood. 2019; 134(11): 860-866.

10. Schuster SJ, Dickinson MJ, Dreyling M, et al. Efficacy and safety of tisagenlecleucel (tisa-cel) in adult patients (Pts) with relapsed/refractory follicular lymphoma (r/r FL): Primary analysis of the phase 2 Elara trial. Oral abstract #7508. 2021 American Society of Clinical Oncology (ASCO) Annual Meeting; Jun 7, 2021; Virtual.
11. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med. 2018 Feb 1;378(5):439-448.
12. Fowler NH, Dickinson M, Dreyling M, et al. Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial. Nature Medicine 2022; 28(2), 325-332.

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
Q2042	Tisagenlecleucel, up to 600 million car-positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2019 annual review: added minimum ALC requirement per manufacturer and clinical trial exclusion criteria; added criteria for LBCL; added hematologist prescriber option; references reviewed and updated.	01/2019	
2Q 2019: LBCL: Removed requirement for CD19 tumor expression.	04/2019	
1Q 2020 annual review: Appendix D was updated to include information related to CNS disease; added requirement in Section IA and IB to confirm "Member does not have active or primary central nervous system (CNS) disease"; ALL: per NCCN treatment guidelines and clinical trial inclusion criteria modified previous therapy requirement to require one of the following (a, b, or c): a) Disease is refractory or member has had ≥ 2 relapses; b) Disease is Philadelphia chromosome positive: failure of 2 lines of chemotherapy that included 2 tyrosine kinase inhibitors; c) Member has relapsed following HSCT and must be ≥ 6 months from HSCT at the time of Kymriah infusion; updated therapeutic alternatives to include regimens for Ph-negative ALL; added HCPCS codes; references reviewed and updated.	01/2020	
1Q 2021 annual review: clarified acceptable types of LBCL diagnoses per FDA indication and NCCN compendium; for	01/2021	

Reviews, Revisions, and Approvals	Date	P&T Approval Date
ALL removed exclusion for active CNS disease per NCCN support for use in extramedullary disease; references reviewed and updated.		
1Q 2022 annual review: to align with other CAR-T policies, added requirement that member has not previously received CAR-T therapy and Kymriah is not prescribed concurrently with other CAR-T therapy; for ALL clarified that hematopoietic stem cell transplantation should more specifically refer to allogeneic stem cell transplantation; references reviewed and updated.	01/2022	
1Q 2023 annual review: added new FDA approved indication: r/r FL after 2 or more lines of systemic therapy; for LBCL added NCCN supported use in AIDS-related DLBCL, primary effusion lymphoma, and HHV8-positive DLBCL; references reviewed and updated.	01/2023	