EVH Clinical Guideline 2723.CC for Car-T Therapy

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STATEMENT

General Information

- *It is an expectation that all patients receive care/services from a licensed clinician. All appropriate supporting documentation, including recent pertinent office visit notes, laboratory data, and results of any special testing must be provided. If applicable: All prior relevant imaging results and the reason that alternative imaging cannot be performed must be included in the documentation submitted.*
- *Where a specific clinical indication is not directly addressed in this guideline, medical necessity determination will be made based on widely accepted standard of care criteria. These criteria are supported by evidence-based or peer-reviewed sources such as medical literature, societal guidelines, and state/national recommendations.*
- *The guideline criteria in the following sections were developed utilizing evidence-based and peer-reviewed resources from medical publications and societal organization guidelines as well as from widely accepted standard of care, best practice recommendations.*

INDICATIONS

This policy includes:

- Tisagenlecleucel (Kymriah)
- Axicabtagene Ciloleucel (Yescarta)
- Brexucabtagene Autoleucel (Tecartus)
- Lisocabtagene Maraleucel (Breyanzi)
- Idecabtagene Vicleucel (Abecma)
- Ciltacabtagene Autoleucel (Carvykti)
- Obecabtagene Autoleucel (Aucatzyl)

Indications for Immune Effector Cell Therapy (IECT) [1]

Tisagenlecleucel (Kymriah) [2]

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

- Pediatric and young adult members (up to 25 years of age) with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse
    - Members have experienced disease relapse after allogeneic stem cell transplantation (SCT) and member is ≥ 6 months from above transplantation at the time of infusion; **OR**
    - Members have relapsed/refractory Philadelphia chromosome-negative B-ALL that

has progressed after 2 cycles of a standard chemotherapy regimen for initial diagnosis or after 1 cycle of standard chemotherapy for relapsed leukemia; **OR**

- Members have relapsed/refractory Philadelphia chromosome-positive B-ALL that has progressed after failure of 2 prior regimens, including a Tyrosine Kinase Inhibitor (TKI)-containing regimen

- Adult members with relapsed or refractory (r/r) 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
  - Members must have previously received at least two lines of therapy (including rituximab and an anthracycline (for DBCL)) **AND**
  - Either having failed autologous hematopoietic stem cell transplantation (ASCT) or being ineligible for or not consenting to ASCT
- Adult members with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy (including an anti-CD20 antibody and an alkylating agent) OR autologous hematopoietic stem cell transplant (HSCT). 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)
- Members must present CD19 tumor expression
- Members must not have received prior CD19-directed chimeric antigen receptor (CAR) T-cell therapy
- Delay tisagenlecleucel infusion if member has unresolved serious adverse reaction from preceding chemotherapies (e.g., pulmonary reactions, cardiac reactions, hypotension), active uncontrolled infection, active graft versus host disease (GVHD), or worsening of leukemia burden following lymphodepleting chemotherapy

NOTE: Tisagenlecleucel is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIAH REMS due to the risk of cytokine release syndrome (CRS) and neurological toxicities.

Axicabtagene Ciloleucel (Yescarta) [3]

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

- Adult members (18 years of age or older) with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy or disease progression or relapse less ≤12 months after autologous stem-cell transplantation (ASCT); including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
- Adult members with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy

- Adult members with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy that must have included a combination of anti-CD20 monoclonal antibody (e.g. rituximab); and an alkylating agent (e.g. bendamustine, cyclosphamide) containing regimen; or disease progression or relapse less ≤12 months after autologous stem-cell transplantation (ASCT). This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s)
- Members must present CD19 tumor expression
- Members must not have received prior CD19-directed chimeric antigen receptor (CAR) T-cell therapy
- Members must not have evidence of active infection or inflammatory disorders

NOTE: Axicabtagene ciloleucel (Yescarta) is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA and TECARTUS REMS due to the risk of CRS and neurological toxicities.

Brexucabtagene Autoleucel (Tecartus) [4]

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

- Adult members (18 years of age and above) with relapsed or refractory mantle cell lymphoma (MCL) who had previously received the following treatments, but are not limited to:
    - Anthracycline or bendamustine-containing chemotherapy; and
    - Anti-CD20 monoclonal antibody therapy (e.g., rituximab); and
    - Bruton's tyrosine kinase inhibitor (BTKi) therapy (e.g., ibrutinib, acalabrutinib, zanubrutinib)

  This indication is approved under accelerated approval based on overall response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- Adult members with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)
- Members must present CD19 tumor expression
- Members must not have received prior CD19-directed chimeric antigen receptor (CAR) T-cell therapy
- Members must not have evidence of active infection or inflammatory disorders

NOTE: Brexucabtagene autoleucel is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) due to the risk of CRS and neurological toxicities.

Lisocabtagene maraleucel (Breyanzi) [5]

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

- Adult members with large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B who EITHER have:
    - Refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy
    - Refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age
    - Relapsed or refractory disease after 2 or more lines of systemic therapy
- Adult members with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have received at least 2 prior lines of therapy, including a Bruton tyrosine kinase (BTK) inhibitor and a B-cell lymphoma 2 (BCL-2) inhibitor. 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)
- Adult members with relapsed or refractory follicular lymphoma (FL) who have received 2 or more prior 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)
- Adult members with relapsed or refractory mantle cell lymphoma (MCL) who have received at least 2 prior lines of systemic therapy, including a Bruton tyrosine kinase (BTK) inhibitor
- Delay lisocabtagene maraleucel infusion if member has unresolved serious adverse reaction from preceding chemotherapies, active uncontrolled infection, or active graft versus host disease (GVHD)
- Members must present CD19 tumor expression
- Members must not have received prior CD19-directed chimeric antigen receptor (CAR) T-cell therapy.

NOTE: Lisocabtagene maraleucel (Breyanzi(R)) is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the BREYANZI REMS due to the risk of CRS and neurologic toxicities.

Idecabtagene vicleucel (Abecma) [6]

ABECMA is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy indicated for the treatment of:

- Adult members with relapsed or refractory multiple myeloma after two or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody
- Delay idecabtagene vicleucel for up to 7 days if member has unresolved serious adverse

events (especially pulmonary events, cardiac events, or hypotension), including those after preceding chemotherapies OR if member has active infections or inflammatory disorders

- Members must not have received prior chimeric antigen receptor (CAR) T-cell therapy

NOTE: Idecabtagene vicleucel is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ABECMA REMS due to the risk of CRS and neurological toxicities.

Ciltacabtagene autoleucel (Carvykti) [7]

CARVYKTI is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy indicated for the treatment of:

- Adult members with relapsed or refractory multiple myeloma after at least one prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent, and are refractory to lenalidomide
- Delay ciltacabtagene autoleucel if member has ANY of the following conditions:
  - Clinically significant active infection or inflammatory disorders
  - Grade ≥3 non-hematologic toxicities of cyclophosphamide and fludarabine conditioning, except for Grade 3 nausea, vomiting, diarrhea, or constipation. CARVYKTI infusion should be delayed until resolution of these events to Grade ≤1

NOTE: Ciltacabtagene autoleucel is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the CARVYKTI REMS due to the risk of CRS and neurologic toxicities.

Obecabtagene Autoleucel (Aucatzyl) [8]

AUCATZYL is a genetically modified T cell immunotherapy indicated for the treatment of:

- Adult members with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)
- Delay AUCATZYL treatment if the member is experiencing severe intercurrent infection
  - If the member requires supplementary oxygen, AUCATZYL should only be infused if considered appropriate based on the treating physician's benefit/risk assessment
  - A delay to the second split may be required to manage toxicities

NOTE: Members should be monitored for CRS and immune effector cell-associated neurotoxicity syndrome (ICANS).

LIMITATIONS

- KYMRIAH is not indicated for treatment of members with primary central nervous system lymphoma [2]
- YESCARTA is not indicated for the treatment of members with primary central nervous

system lymphoma [3]

- TECARTUS is not indicated for the treatment of members with primary central nervous system lymphoma [4]
- BREYANZI is not indicated for the treatment of members with primary central nervous system lymphoma [5]
- Car-T Therapy is authorized once per lifetime
- The treating facility is certified under the Risk Evaluation and Mitigation Strategy (REMS) System program appropriate to requested CAR-T product

CODING AND STANDARDS

Codes

Code	Description
38225	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
38226	Chimeric antigen receptor T-cell (CAR-T) therapy; preparation of blood-derived T lymphocytes for transportation (e.g., cryopreservation, storage)
38227	Chimeric antigen receptor T-cell (CAR-T) therapy; receipt and preparation of CAR-T cells for administration
38228	Chimeric antigen receptor T-cell (CAR-T) therapy; CAR-T cell administration, autologous
C9399	Unclassified drugs or biologicals Abecma (idecabtagene vicleucel) received FDA approval on March 26, 2021. CMS has not yet assigned a HCPCS Level II code to this product. Until that time, report this biological with C9399 Unclassified drugs or biologicals. This code is used to bill newly approved products prior to assignment of a specific HCPCS Level II code.
J3590	Unclassified biologics
J9999	Not otherwise classified, antineoplastic drugs
Q2041	Axicabtagene ciloleucel, up to 200 million autologous anti-CD19 car positive viable T cells, including leukapheresis and dose preparation procedures, per therapeutic dose

Code	Description
Q2042	Tisagenlecleucel, up to 600 million car-positive viable T cells, including leukapheresis and dose preparation procedures, per therapeutic dose
Q2053	Brexucabtagene autoleucel, up to 200 million autologous anti-CD19 CAR positive viable T cells, including leukapheresis and dose preparation procedures, per therapeutic dose
Q2054	Lisocabtagene maraleucel, up to 110 million autologous anti-CD19 CAR-positive viable T cells, including leukapheresis and dose preparation procedures, per therapeutic dose
Q2055	Abecma® (idecabtagene vicleucel)
Q2056	Ciltacabtagene autoleucel, up to 100 million autologous B-cell maturation antigen (BCMA) directed CAR-positive T cells, including leukapheresis and dose preparation procedures, per therapeutic dose
Q2058	Obecabtagene autoleucel, 10 up to 400 million CD19 CAR-positive viable T cells, including leukapheresis and dose preparation procedures, per infusion
S2107	Adoptive immunotherapy i.e., development of specific antitumor reactivity (e.g., tumor-infiltrating lymphocyte therapy) per course of treatment

Applicable Lines of Business

☐	CHIP (Children's Health Insurance Program)
☐	Commercial
☐	Exchange/Marketplace
☒	Medicaid
☐	Medicare Advantage

BACKGROUND

Cancer immunotherapy is a treatment that uses a member's immune system to attack tumors. One type of cancer immunotherapy is Chimeric antigen receptor (CAR) T-cell therapy. This therapy takes T-cells from a member's blood, then using a disarmed virus, the T cells are genetically engineered to produce receptors on their surface called chimeric antigen receptors, or CARs. These special receptors allow the T cells to recognize and attach to a specific protein,

or antigen, on tumor cells. The final step is the infusion of the CAR-T cells into the member (which is preceded by a "lymphodepleting" chemotherapy regimen). The CAR-T cells recognize and kill cancer cells that harbor the antigen on their surfaces.

Side Effects

Like all cancer treatments, CAR-T Cell Therapy has potential side effects, which are sometimes fatal. One of the most common side effects of CAR-T Cell Therapy is Cytokine Release Syndrome (CRS). CRS can result in severe nausea, high fevers and large drops in blood pressure due to the massive release of cytokines into the bloodstream; this side effect can be managed with standard therapies to treat inflammatory conditions, including steroids.

Another potential side effect of CAR T-Cell Therapy is a mass die off of B cells, known as B-cell aplasia. Members with B-cell aplasia must receive immunoglobulin therapy, which provides the necessary antibodies to fight off infections.

There is the potential for neurotoxicity, from cerebral edema to confusion or seizure-like activity.

Other serious side effects include allergic reactions during the infusion, electrolyte abnormalities and low blood cell counts.

POLICY HISTORY

Date	Summary
November 20, 2025	• This guideline replaces PA.216.CC Car-T Therapy • Editorial changes to match the formatting and layout of the new template, no changes to clinical content

LEGAL AND COMPLIANCE

Guideline Approval

Committee

Reviewed / Approved by Evolent Administrative Services Medical Policy Committee

Disclaimer

Evolent Clinical Guidelines do not constitute medical advice. Treating health care professionals are solely responsible for diagnosis, treatment, and medical advice. Evolent uses Clinical Guidelines in accordance with its contractual obligations to provide utilization management. Coverage for services varies for individual members according to the terms of their health care coverage or government program. Individual members' health care coverage may not utilize some Evolent Clinical Guidelines. Evolent clinical guidelines contain guidance that requires prior authorization and service limitations. A list of procedure codes, services or drugs may not be all

inclusive and does not imply that a service or drug is a covered or non-covered service or drug. Evolent reserves the right to review and update this Clinical Guideline in its sole discretion. Notice of any changes shall be provided as required by applicable provider agreements and laws or regulations. Members should contact their Plan customer service representative for specific coverage information.

REFERENCES

1. Kanate AS, Majhail N, DeFilipp Z, et al. Updated Indications for Immune Effector Cell Therapy: 2023 Guidelines from the American Society for Transplantation and Cellular Therapy. Transplant Cell Ther. 2023;29(10):594-597. doi:10.1016/j.jtct.2023.07.002
2. KYMRIAH® (tisagenlecleucel). Package insert. Novartis. U.S. Food and Drug Administration. 2017. **https://www.fda.gov/media/107296/download**
3. YESCARTA® (axicabtagene ciloleucel). Package insert. Kite Pharma, Inc. U.S. Food and Drug Administration. 2024. **https://www.fda.gov/media/108377/download**
4. TECARTUS® (brexucabtagene autoleucel). Package insert. Kite Pharma, Inc. U.S. Food and Drug Administration. 2024. **https://www.fda.gov/media/140409/download**
5. BREYANZI® (lisocabtagene maraleucel). Package insert. Juno Therapeutics, Inc., a Bristol-Myers Squibb Company. U.S. Food and Drug Administration. May 2024. **https://www.fda.gov/media/145711/download**
6. ABECMA® (idecabtagene vicleucel). Package insert. Celgene Corporation, a Bristol-Myers Squibb Company. U.S. Food and Drug Administration. April 2024. **https://www.fda.gov/media/147055/download**
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