MEDICAL COVERAGE GUIDELINES
SECTION: DRUGS

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ARCHIVE DATE:

KYMRIAH™ (tisagenlecleucel)

Non-Discrimination Statement and Multi-Language Interpreter Services information are located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Medical Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Medical Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Medical Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Medical Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

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Description:

The spontaneous regression of certain cancers (e.g., renal cell carcinoma, melanoma) supports the idea that an individual's immune system can delay tumor progression and, on rare occasions, can eliminate tumors altogether. These observations have led to research into various immunologic therapies designed to stimulate an individual's own immune system. Adoptive immunotherapy is a method of activating lymphocytes and/or other types of cells for the treatment of cancer and other diseases. Cells are removed from the individual, processed for some period of time, and then infused back into the individual.

Chimeric antigen receptor T (CAR T) cells are a form of genetically modified autologous immunotherapy that can be directed at B cell precursor acute lymphoblastic leukemia (ALL). This customized treatment uses the individual's own T lymphocytes, which are genetically modified (transfected) with a gene that encodes a chimeric antigen receptor to direct the individual's T cells against the leukemic cells. The T cells are genetically modified ex-vivo, expanded in a production facility, and then infused back into the individual as therapy.

Kymriah is a CD19-directed genetically modified autologous chimeric antigen receptor T cell (CAR T cell) immunotherapy indicated for the treatment of individuals up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

Initial treatment of ALL includes induction therapy with a combination of vincristine, antharacyclines (e.g. daunorubicin, doxorubicin), and corticosteroids with or without L-asparaginase and/or cyclophosphamide. Additionally, intrathecal antimetabolites such as methotrexate, cytarabine, and/or 6-mercaptopurine are often included at induction therapy for CNS prophylaxis. The goal of induction therapy is to achieve complete remission (CR).

For individuals who achieve CR, post-induction consolidation therapy followed by maintenance therapy is recommended.

Individuals who do not achieve CR following induction therapy are considered to have primary refractory disease. Treatment options for individuals who have primary refractory ALL or for individuals who have relapsed following initial or subsequent CR may be managed using repeat chemotherapy (in combination with tyrosine kinase inhibitor for individuals who are Philadelphia Chromosome positive), blinatumomab or inotuzumab (depending on CD tumor expression), or tisagenlecleucel (for refractory ALL or second or later relapsed ALL).

KYMRIAH (tisagenlecleucel) (cont.)

Definitions:

Central nervous system (CNS) Disease for B-Cell Acute Lymphoblastic Leukemia (ALL):
CNS disease for B-cell ALL is defined by the following groups:

- **CNS 1:** Absence of blasts on cerebrospinal fluid cytospin preparation, regardless of the white blood cell (WBC) count
- **CNS 2:** WBC count of less than 5/mL and blasts on cytospin findings
- **CNS 3:** WBC count of 5/mL or more and blasts on cytospin findings and/or clinical signs of CNS leukemia (e.g., facial nerve palsy, brain/eye involvement, hypothalamic syndrome)

Refractory Acute Lymphoblastic Leukemia (ALL):
Refractory (resistant) ALL disease is defined as those individuals who fail to obtain complete response with induction therapy, i.e., failure to eradicate all detectable leukemia cells (<5% blasts) from the bone marrow and blood with subsequent restoration of normal hematopoiesis (>25% marrow cellularity and normal peripheral blood counts).

Relapsed Acute Lymphoblastic Leukemia (ALL):
Relapsed ALL disease describes the reappearance of leukemia cells in the bone marrow or peripheral blood after the attainment of a complete remission with chemotherapy and/or allogeneic cell transplant.

Risk Evaluation and Mitigation Strategies (REMS):
Use of Kymriah is subject to a Risk Evaluation and Mitigation Strategies (REMS) program that requires provider, patient, and dispensing pharmacy be enrolled into the program. Only providers and Pharmacies enrolled into the REMS may prescribe and dispense the drug, respectively, to individuals who are also in the program. A REMS program attempts to manage known or potentially serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) for some drugs to ensure that the benefits of a drug outweigh its risks.

- Health care facilities that dispense and administer tisagenlecleucel must be enrolled and comply with the REMS requirements.
- Certified health care facilities must have onsite, immediate access to tocilizumab, and ensure that a minimum of 2 doses of tocilizumab are available for each patient for administration within 2 hours after tisagenlecleucel infusion, if needed for treatment of cytokine release syndrome.
- Certified health care facilities must ensure that health care providers who prescribe, dispense or administer tisagenlecleucel are trained about the management of cytokine release syndrome and neurologic toxicities.

KYMRIAH (tisagenlecleucel) (cont.)

Criteria:

For gene therapy other than Kymriah, refer to BCBSAZ Medical Coverage Guideline #O680, *"Gene Therapy".*

For adoptive immunotherapy and chimeric antigen receptor T (CAR T) cell immunotherapy other than Kymriah, refer to BCBSAZ Medical Coverage Guideline #O368, *"Immunotherapy, Adoptive".*

Requests for Kymriah will be reviewed by the medical director(s) and/or clinical advisor(s).

See Resources section for FDA-approved dosage.

KYMRIAH IS AVAILABLE ONLY THROUGH A RESTRICTED PROGRAM UNDER A RISK EVALUATION AND MITIGATION STRATEGY (REMS) CALLED THE KYMRIAH REMS PROGRAM.

- Kymriah is considered ***medically necessary*** for the treatment of individuals 25 years of age and younger with acute lymphoblastic leukemia (ALL) with morphologic bone marrow tumor involvement (≥ 5% lymphoblasts) with documentation of **ALL** of the following:

  1. The individual has a confirmed CD19-positive B-cell precursor ALL
  2. Individual has **ONE** of the following:

     - Refractory ALL (failed to achieve a complete response) after treatment with **two** cycles of standard chemotherapy **OR**
     - Relapsed ALL (achieved a complete response) and has experienced **two** or more relapses after **two** or more cycles of standard chemotherapy

  3. Philadelphia chromosome (Ph) test result is **ONE** of the following:

     - If ALL is Ph-positive, **BOTH** of the following:

       a. There have been **two or more** relapses **and** failure, contraindication, or intolerance to **two** TKIs (e.g., Gleevec® [imitinib], Iclusig® [ponatinib], Sprycel™ [dasatinib], Tasigna® [nilotinib])
       b. There is documentation of failure, contraindication, or intolerance to Blincyto® (blinatumomab)

     - If ALL is Ph-negative, there is documentation of failure, contraindication, or intolerance to Blincyto (blinatumomab)

  4. Have not received prior treatment with tisagenlecleucel or any other gene therapy or are being considered for treatment with any other gene therapy

KYMRIAH (tisagenlecleucel) (cont.)

Criteria: (cont.)

- Kymriah is considered ***medically necessary*** for the treatment of individuals 25 years of age and younger with acute lymphoblastic leukemia (ALL) with morphologic bone marrow tumor involvement (≥ 5% lymphoblasts) with documentation of **ALL** of the following: (cont.)

  5. Adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis
  6. Absence of **ALL** of the following:

     - Burkitt lymphoma
     - Active hepatitis B, C, or any uncontrolled infection
     - Grade 2 to 4 graft-versus-host disease
     - Concomitant genetic syndrome with the exception of Down syndrome
     - Received allogeneic cellular therapy, such as donor lymphocyte infusion within 6 weeks prior to tisagenlecleucel infusion
     - Active central nervous system 2 or 3 acute lymphoblastic leukemia (i.e., white blood cell count ≥ 5 cells/µL in cerebrospinal fluid with presence of lymphoblasts)

- Kymriah for all other indications not previously listed or if above criteria not met is considered ***experimental or investigational*** based upon:

  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

  These indications include, *but are not limited to:*

  - Treatment with dosing or frequency outside the FDA-approved dosing and frequency

KYMRIAH (tisagenlecleucel) (cont.)

Resources:

Literature reviewed 02/01/18. We do not include marketing materials, poster boards and non-published literature in our review.

The BCBS Association Medical Policy Reference Manual (MPRM) policy is included in our guideline review. References cited in the MPRM policy are not duplicated on this guideline.

1. 8.01.01 BCBS Association Medical Policy Reference Manual. Adoptive Immunotherapy. Re-issue date 12/14/2017, issue date 12/01/1996.

2. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Acute Lymphoblastic Leukemia 2017.4. 09/27/2017.

3. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Acute Lymphoblastic Leukemia 2017.5. 10/27/2017.

4. UpToDate. Treatment of relapsed or refractory acute lymphoblastic leukemia in adults. Last updated 09/08/2017.

KYMRIAH (tisagenlecleucel) (cont.)

Resources: (cont.)

Kymriah Package Insert:

- FDA-approved indication and dosage:

Indication	Recommended Dose
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	For autologous use and intravenous use only. Dosing is based on the number of chimeric antigen receptor (CAR) positive viable T cells. For patients 50 kg or less, administer 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg body weight intravenously. For patients above 50 kg, administer 0.1 to 2.5 x 10^8 total CAR-positive viable T cells (non-weight based) intravenously. Tisagenlecleucel has a black box warning because of the risk of cytokine release syndrome and neurologic toxicities that include fatal or life-threatening reactions. It should not be administered to patients with active infection or inflammatory disorders. It is recommended that severe or life-threatening cytokine release syndrome should be treated with tocilizumab. Patients should be monitored for neurologic events after treatment. Verify availability of tocilizumab prior to infusion.

Initial Approval:
Approve 1 unit of tisagenlecleucel, up to 250 million CAR-positive viable T cells, including leukapheresis and dose preparation procedures, per infusion for a one-time treatment course per lifetime

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

KYMRIAH (tisagenlecleucel) (cont.)

Non-Discrimination Statement:

Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ's Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ's Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html

Multi-Language Interpreter Services:

Spanish: Si usted, o alguien a quien usted está ayudando, tiene preguntas acerca de Blue Cross Blue Shield of Arizona, tiene derecho a obtener ayuda e información en su idioma sin costo alguno. Para hablar con un intérprete, llame al 602-864-4884.

Navajo: Díí kwe'é atah nílínigíí Blue Cross Blue Shield of Arizona haada yit'éego bína'ídíłkidgo éí doodago Háida bíjá anilyeedígíí t'áadoo le'é yína'ídíłkidgo beehaz'áanii hóló díí t'áá hazaadk'ehjí háká a'doowołgo bee haz'ą doo bąąh ílínígóó. Ata' halne'ígíí kojį' bich'į' hodíilnih 877-475-4799.

Chinese: 如果您，或是您正在協助的對象，有關於插入項目的名稱 Blue Cross Blue Shield of Arizona 方面的問題，您有權利免費以您的母語得到幫助和訊息。洽詢一位翻譯員，請撥電話 在此插入數字 877-475-4799。

Vietnamese: Nếu quý vị, hay người mà quý vị đang giúp đỡ, có câu hỏi về Blue Cross Blue Shield of Arizona quý vị sẽ có quyền được giúp và có thêm thông tin bằng ngôn ngữ của mình miễn phí. Để nói chuyện với một thông dịch viên, xin gọi 877-475-4799.

Arabic:
إن كان لديك أو لدى شخص تساعده أسئلة بخصوص Blue Cross Blue Shield of Arizona، فلديك الحق في الحصول على المساعدة والمعلومات الضرورية بلغتك من دون اية تكلفة. للتحدث مع مترجم اتصل ب 877-475-4799.

KYMRIAH (tisagenlecleucel) (cont.)

<u>Multi-Language Interpreter Services</u>: (cont.)

Tagalog: Kung ikaw, o ang iyong tinutulangan, ay may mga katanungan tungkol sa Blue Cross Blue Shield of Arizona, may karapatan ka na makakuha ng tulong at impormasyon sa iyong wika ng walang gastos. Upang makausap ang isang tagasalin, tumawag sa 877-475-4799.

Korean: 만약 귀하 또는 귀하가 돕고 있는 어떤 사람이 Blue Cross Blue Shield of Arizona 에 관해서 질문이 있다면 귀하는 그러한 도움과 정보를 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 그렇게 통역사와 얘기하기 위해서는 877-475-4799 로 전화하십시오.

French: Si vous, ou quelqu'un que vous êtes en train d'aider, a des questions à propos de Blue Cross Blue Shield of Arizona, vous avez le droit d'obtenir de l'aide et l'information dans votre langue à aucun coût. Pour parler à un interprète, appelez 877-475-4799.

German: Falls Sie oder jemand, dem Sie helfen, Fragen zum Blue Cross Blue Shield of Arizona haben, haben Sie das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Um mit einem Dolmetscher zu sprechen, rufen Sie bitte die Nummer 877-475-4799 an.

Russian: Если у вас или лица, которому вы помогаете, имеются вопросы по поводу Blue Cross Blue Shield of Arizona, то вы имеете право на бесплатное получение помощи и информации на вашем языке. Для разговора с переводчиком позвоните по телефону 877-475-4799.

Japanese: ご本人様、またはお客様の身の回りの方でも、Blue Cross Blue Shield of Arizona についてご質問がございましたら、ご希望の言語でサポートを受けたり、情報を入手したりすることができます。料金はかかりません。通訳とお話される場合、877-475-4799 までお電話ください。

Farsi:
اگر شما، یا کسی که شما به او کمک میکنید ، سوال در مورد Blue Cross Blue Shield of Arizona ، داشته باشید حق این را دارید که کمک و اطلاعات به زبان خود را به طور رایگان دریافت نمایید 877-475-4799
[تماس حاصل نمایید.

Assyrian:
[illegible] Blue Cross Blue Shield of Arizona [illegible]
[illegible] 877-475-4799.

Serbo-Croatian: Ukoliko Vi ili neko kome Vi pomažete ima pitanje o Blue Cross Blue Shield of Arizona, imate pravo da besplatno dobijete pomoć i informacije na Vašem jeziku. Da biste razgovarali sa prevodiocem, nazovite 877-475-4799.

Thai: หากคุณ หรือคนที่คุณกำลังช่วยเหลือมีคำถามเกี่ยวกับ Blue Cross Blue Shield of Arizona
คุณมีสิทธิที่จะได้รับความช่วยเหลือและข้อมูลในภาษา ของคุณได้โดยไม่มีค่าใช้จ่าย พูดคุยกับล่าม โทร 877-475-4799