BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

EVIDENCE-BASED CRITERIA	**ORIGINAL EFFECTIVE DATE: 05/16/24**
SECTION: SPECIALTY MEDICAL DRUGS	**LAST REVIEW DATE:**
	CURRENT EFFECTIVE DATE: 05/16/24
	LAST CRITERIA REVISION DATE:
NEXT ANNUAL REVIEW DATE: 2ND QTR 2025	**ARCHIVE DATE:**

TUMOR INFILTRATING LYMPHOCYTE (TIL) THERAPY FOR UNRESECTABLE AND METASTATIC MELANOMA

- **AMTAGVI™ (lifileucel)**

Non-Discrimination Statement is 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 Evidence-Based Criteria must be read in its entirety to determine coverage eligibility, if any.

This Evidence-Based Criteria 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.

Evidence-Based Criteria are subject to change as new information becomes available.

For purposes of this Evidence-Based Criteria, the terms "experimental" and "investigational" are considered to be interchangeable.

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Criteria:

Refer to FDA website for current indications and dosage.

- **Criteria for initial therapy:** Amtagvi (lifileucel) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

  2. Individual is 18 years of age or older

  3. Individual has a confirmed diagnosis of **ONE** of the following:

     - Unresectable or metastatic melanoma with **ALL** of the following:

       a. Defined as Stage IIIc or Stage IV cutaneous melanoma
       b. Previously treated with a PD-1 blocking antibody (e.g., nivolumab, pembrolizumab)
       c. If BRAF V600 mutation positive, previously treated with a BRAF inhibitor (e.g., atezolizumab, dabrafenib, encorafenib, vemurafenib) with or without a MEK inhibitor (e.g., cobimetinib, trametinib)

     - Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

  4. Individual meets **ALL** of the following:

     - There is a negative pregnancy test in a woman of childbearing potential
     - Eastern Cooperative Oncology Group (ECOG) performance status is 0 or 1

  5. Individual does **NOT** have **ANY** of the following:

     - Prior organ allograft or cell transfer therapy (e.g., CAR-T, TIL therapy, etc.)
     - History of melanoma of uveal/ocular origin
     - Untreated brain metastases
     - Chronic systemic corticosteroid therapy
     - Uncontrolled infection
     - Left ventricular ejection fraction (LVEF) less than 45 percent or New York Heart Association (NYHA) functional classification greater than class 1
     - Forced expiratory volume in one second (FEV1) of less than or equal to 60 percent

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Approval duration: One-time treatment infusion per lifetime for any TIL therapy treatment

Renewal Information: Continued therapy will not be authorized for any TIL therapy treatment

- Amtagvi (lifileucel) for all other indications not previously listed is considered ***experimental or investigational*** and will not be approved when any **ONE** or more of the following criteria are met:

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

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

- Treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, or duration.

Description:

Amtagvi (lifileucel) is a tumor-derived autologous T cell immunotherapy indicated for the treatment of adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor. This indication is approved under accelerated approval based on objective response rate (ORR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Amtagvi is only available at Authorized Treatment Centers. It is manufactured from resected patient tumor tissue that are sent to the manufacturer. Immune cells from the tumor are expanded in cell culture, washed, formulated as a cell suspension and cryopreserved. Prior to administration of Amtagvi, the individual will receive lymphodepleting chemotherapy regimen of cyclophosphamide 60 mg/kg intravenously with mesna daily for 2 days followed by fludarabine 25 mg/m2 intravenously daily for 5 days. Amtagvi is administered 24 hours to 4 days after the last dose of fludarabine in an inpatient hospital setting with an intensive care facilitly. Intravenous IL-2 (aldesluekin) is administered 3-24 hours after Amtagvi to support cell expansion *in-vivo*.

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Definitions:

Pathological Staging (pTNM)

	T	M	N
Stage 0*	Tis	N0	M0
Stage 1A	T1a	N0	M0
	T1b	N0	M0
Stage 1B	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T3a	N0	M0
Stage IIB	T3b	N0	M0
	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage IIIA	T1a/b, T2a	N1a, N2a	M0
Stage IIIB	T0	N1b, N1c	M0
	T1a/b, T2a	N1b/c, N2b	M0
	T2b, T3a	N1a/b/c, N2a/b	M0
Stage IIIC	T0	N2b/c, N3b/c	M0
	T1a/b, T2a/b, T3a	N2c, N3a/b/c	M0
	T3b, T4a	Any N ≥ N1	M0
	T4b	N1a/b/c, N2a/b/c	M0
Stage IIID	T4b	N3a/b/c	M0
Stage IV	Any T, Tis	Any N	M1

AJCC Cancer Staging Manuel, Eighth Edition (2017)
Pathological staging includes microstaging of the primary melanoma, including any additional staging information from the wide-excision (surgical) specimen that constitutes primary tumor surgical treatment and pathological information about the regional lymph nodes after SLN biopsy or therapeutic lymph node dissection for clinically evident regional lymph node disease.
*Pathological Stage 0 and pathological T1 without clinically detected regional or distant metastases (pTis/pT1 cN0 cM0) do not require pathological evaluation of lymph nodes to complete pathological staging; use cN0 to assign pathological stage.

ECOG Performance Status Table:

Eastern Co-operative Oncology Group (ECOG) Performance Status	
Grade	ECOG description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

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Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982

History:	**Date:**	**Activity:**
Pharmacy and Therapeutics Committee	05/16/24	Reviewed and approved guideline
Clinical Pharmacist	03/04/24	Development

Coding:

HCPCS: C9399/J9999

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Resources:

Literature reviewed 05/16/24. We do not include marketing materials, poster boards and non-published literature in our review.

1. Amtagvi (lifileucel). Product information, revised by Iovance Biotherapeutics Manufacturing LLC 02/2024, at DailyMed https://dailymed.nlm.nih.gov/dailymed/ Accessed March 4. 2024.

2. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Melanoma: Cutaneous Version 1.2024. Updated February 12, 2024. Available at: http://www.nccn.org. Accessed March 25. 2024.

3. Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions. https://www.azleg.gov/ars/20/00826.htm.

4. Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions. https://www.azleg.gov/ars/20/01057.htm.

5. Sosman JA. Systemic treatment of metastatic melanoma lacking a BRAF mutation. In: UpToDate, Atkins MB, Yushak M (Eds). UpToDate, Waltham, MA.: Available at http://uptodate.com. Topic last updated March 14, 2024. Accessed March 25, 2024.

6. Sosman JA. Systemic treatment of metastatic melanoma with BRAF and other molecular alterations. In: UpToDate, Atkins MB, Yushak M (Eds). UpToDate, Waltham, MA.: Available at http://uptodate.com. Topic last updated March 14, 2024. Accessed March 25, 2024.

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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