Tumor-Infiltrating Lymphocyte (TIL) Cell Therapy

Clinical Guidelines
UN-CSTRANSPT005.A

Ohio Only

Effective Date: 03/01/2026

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Guideline Application

This clinical guideline applies only to the state of Ohio. Any requests for services that are stated as unproven or services for which there is a coverage or quantity limit will be evaluated for medical necessity using Rule 5160-1-01 - Ohio Administrative Code | Ohio Laws

The Ohio Hematopoietic Transplant and Cellular Therapy Consortium is a consortium that ensures all Ohio residents have access to quality care for hematologic malignancies. The Consortium identifies patients for transplant based on patient selection criteria and clinical summaries. Reimbursement for cellular therapy is contingent upon review and the recommendation by the Ohio Hematopoietic Transplant and Cellular Therapy Consortium | Galena, OH | Cause IQ

Prior authorization activities must be conducted in accordance with the Ohio Department of Medicaid Managed Care Provider Agreements located at: Managed Care Agreements (ohio.gov)

Introduction

Tumor-infiltrating lymphocyte (TIL) cell therapy involves surgical resection of a patient's tumor, *ex vivo* TIL expansion under conditions that overcome immunosuppressive responses elicited by the tumor and the tumor microenvironment, administration of a lymphodepleting regimen, and infusion of the final TIL product back into the patient followed by interleukin-2 administration to support T-cell activity (Mullinax et al., 2022).

A broad variety of cancer surgical subspecialists may be required to procure tissue for TILs. Selecting the optimal anatomic resection site and the least invasive surgical approach are critical to ensure patients recover adequately before receiving chemotherapy. Therefore, surgical sites that minimize morbidity (e.g. subcutaneous nodules) and that can be performed in the outpatient setting are favored, although superficial lesions may not always yield the required amount of tumor or may need to be avoided to facilitate wound healing. Sites that have been previously irradiated, those with ulcerated tumors, or those with high bacterial growth, leading to contamination of TIL cultures should be avoided (Crompton et al., 2018).

TIL cell therapy is currently being investigated as a treatment for several solid tumor types including, but not limited to, biliary tract cancers (NCT03801083), pretreated metastatic triple negative breast cancer (NCT04111510), pediatric high risk solid tumors (NCT06047977), metastatic non-small-cell lung cancer (NCT04614103), and squamous cell carcinoma of the head & neck (NCT03083873).

The purpose of these guidelines is to identify the indications for and evidence supporting TIL cell therapy. Optum recognizes TIL cell therapy is a rapidly evolving field and makes every effort to apply the most recent clinical data and recommendations to this guideline. Requests for treatment are reviewed on an individual basis and, to the extent possible, consideration will be given to new peer-reviewed, published literature as they become available as well as FDA. Optum encourages providers to supply new, relevant information as indicated.

FDA Approved Agents

Lifileucel (Amtagvi™) is a tumor-derived autologous T cell immunotherapy indicated for the treatment of adult patients with unresectable or metastatic melanoma previously treated with a programmed death 1 (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).

Ohio Medical Necessity

Medical necessity for individuals covered by early and periodic screening, diagnosis and treatment (EPSDT) is criteria of coverage for procedures, items, or services that prevent, diagnose, evaluate, correct, ameliorate, or treat an adverse health condition such as an illness, injury, disease or it's symptoms, emotional or behavioral dysfunction, intellectual deficit, cognitive impairment, or developmental disability. [Ohio Administrative Code 5160-1-01 (A)].

Indications

Advanced Melanoma

Melanoma is the third most common cutaneous malignancy after basal cell and squamous cell carcinoma and ranks as the fifth most common cancer in both sexes. In 2023, approximately 97,610 new invasive melanoma cases and 7,990 deaths were reported in the United States, with incidence highest among individuals of European ancestry and older age groups. Five-year relative survival for melanoma is approximately 94% overall, exceeding 99% for localized disease, 75% for regional spread, and 35% for distant metastases. Prognosis is strongly influenced by metastatic site, with brain and visceral involvement associated with poorer outcomes (Siegel et al., 2023).

Treatment

The treatment of advanced (unresectable or metastatic) melanoma with immune checkpoint inhibitors (ICI) and targeted oncogenic pathway inhibition with BRAF and MEK inhibitors has improved patient outcomes. Forty to 65% of patients with advanced melanoma have primary resistance to ICI. Of those with initial disease control, 30-40% develop acquired resistance (Sarnaik et al., 2021). Approximately 15% to 20% of BRAF V600 mutation-positive patients fail to respond to targeted therapy initially and only 22% remain progression-free at 3 years (Long et al., 2017). While primary resistance is lower in patients treated with PD-1 blocking antibody plus anticytotoxic T-lymphocyte-associated protein 4 (CTLA-4) therapy, 36% of patients discontinue therapy due to treatment-emergent adverse events (TEAEs), with 88% developing immune-related adverse events (irAEs), many of these being persistent. Patients progressing after anti-PD-1 therapy, anti-PD-1 plus anti-CTLA-4 therapy, and targeted agents have limited options with only 4% - 10% achieving objective responses to chemotherapy (Buchbinder et al., 2019). Lifileucel (Amtagvi™) is an autologous TIL therapy that uses tumor-tissue T-cells capable of recognizing tumor antigens and being expanded *ex vivo* while maintaining the heterogeneous repertoire of T-cells, using a centralized manufacturing process (Sarnaik et al., 2021).

The efficacy of a single treatment with Amtagvi was evaluated in a global, multicenter, multicohort, open-label, single-arm clinical study enrolling patients with unresectable or metastatic melanoma who had previously been treated with at least one systemic therapy, including a PD-1 blocking antibody, and, if BRAF V600 mutation-positive, a BRAF inhibitor or BRAF inhibitor with MEK inhibitor. There were 111 patients who underwent tumor resection of who 22 (19.8%) patients did not receive Amtagvi due to the following reasons: Inability to manufacture Amtagvi (n=6), disease-related death (n=3), meeting exclusion criteria (n=5), disease progression (n=3), starting new anti-cancer therapy or consent withdrawal (n=3), or adverse events from lymphodepletion including one death (n=2). Among 89 patients who received Amtagvi, 2 patients were excluded because the product did not meet specifications and 5 patients were excluded due to product comparability. The primary efficacy analysis set included 82 patients who received Amtagvi. Among these, 9 patients received Amtagvi at a dose less than 7.5×10^9 viable cells and did not achieve an objective response. The recommended Amtagvi dosing range was set at 7.5×10^9 to 72×10^9 viable cells (73 patients received this dosing range). Median time from tumor tissue procurement to the end of the manufacturing process was 23 days and to infusion was 34 days.

Patients had to have received at least one line of prior therapy. All 73 patients (100%) patients received prior anti-PD-1 therapy, 63 (86.3%) received prior anti-CTLA-4 therapy, 42 (57.5%) received anti-PD 1/anti-CTLA-4 combination

therapy and 20 (27.4%) received a BRAF inhibitor or combination therapy with BRAF and MEDK inhibitors. Patients received a median of 3 prior lines of therapy and a median of 2 prior lines of anti-PD 1 containing therapies. Amtagvi was administered following a lymphodepleting regimen consisting of cyclophosphamide 60mg/kg daily with mesna for 2 days followed by fludarabine 25 mg/m^2 daily for 5 days. Three to 24 hours after infusion, patients received IL-2 (aldesleukin) at 600,000 IU/kg every 8 to 12 hours for up to 6 doses in order to support cell expansion *in vivo.* Efficacy was established on the basis of the ORR of 31.4%. The median time to best response for those who achieved a partial response or better was 1.5 months (min, max: 1.3, 4.2) [FDA, 2024].

A phase 3, multi-center, open-label trial (Rohann et al., 2022), randomly assigned 168 patients with unresectable stage IIIC or IV melanoma in a 1:1 ratio to receive TILs (*n*=84) or ipilimumab (*n*=84). Nine patients (11%) received TILs as first-line treatment. Randomization was stratified according to *BRAF* V600-mutation status, line of treatment, and treatment center. Infusion of at least 5x10^9 TILs was preceded by nonmyeloablative, lymphodepleting chemotherapy (cyclophosphamide and fludarabine). The primary endpoint was progression-free survival. Median progression-free survival was 7.2 months (95% CI, 4.2 to 13.1) in the TIL group and 3.1 months (95% CI, 3.0 to 4.3) in the ipilimumab group (hazard ratio for progression or death, 0.50; 95% CI, 0.35 to 0.72; P<0.001); 49% (95% CI, 38 to 60) and 21% (95% CI, 13 to 32) of the patients, respectively, had an objective response. Median overall survival was 25.8 months (95% CI, 18.2 to not reached) in the TIL group and 18.9 months (95% CI, 13.8 to 32.6) in the ipilimumab group. Treatment-related adverse events were more frequently seen with TILs than with ipilimumab, owing predominantly to chemotherapy, interleukin-2, or both. Despite the increased frequency of adverse events, the global health-related quality of life scores as measured by the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 15 palliative care (EORTC QLQ-C15 PAL) were higher in patients who received TILS.

Assessment of long-term survival benefit was described by Wermke et al. (2023). Median overall survival (OS) was 13.9 months (95% CI, 10.6-17.8) among all patients with a 4-year OS rate of 47.3 (95% CI, 32.5%-60.7%). Four-year OS rates according to patterns of response were 48.3% in early responders (95% CI, 31.9%-62.9%), 41.7% (95% CI, 10.9%-70.8%) in late responders, 37.2% (95% CI, 21.0%-53.5%) in responders without a deepened response, and 68.2% (95% CI, 39.5%-85.4%) in responders with deepened responses. The longest duration of independent review committee (IRC)-assessed response was ongoing at 55.8 months. Additionally, 4 patients converted to a complete response more than one year after treatment.

NCCN Guidelines for Cutaneous Melanoma® (V2.2025) indicate TIL therapy should be considered for patients with good performance status who have progressed on anti-PD-1 based therapy and BRAF/MEK inhibition (if BRAF V600 mutation present), based on favorable durable response rates in anti-PD-1 refractory melanoma. The indication has a 2A recommendation. The guideline cautions that TIL therapy should not be considered for patients with inadequate cardiac, pulmonary, and/or renal function, poor performance status, or with untreated or active brain metastases. Referral to a TIL-authorized treatment center is recommended.

Additionally, the NCCN Drugs & Biologics Compendium® gives a 2A recommendation for Interleuken-2 (Aldesleukin) as a component of TIL therapy for metastatic or unresectable cutaneous melanoma after progression on anti-PD-1-based therapy and BRAF/MEK inhibitor therapy (if BRAF V600 mutation-positive). Interleukin-2 should not be used in patients with inadequate organ function, poor performance status, or with untreated or active brain metastases. NCCN defines metastatic disease in this instance as including “stage III unresectable/borderline resectable disease with clinically positive node(s) or clinical satellite/in-transit metastases, or/as well as unresectable/borderline resectable local satellite/in-transit recurrence, unresectable nodal recurrence, and widely disseminated distant metastatic disease.”

See Appendix for NCCN Categories of Evidence and Consensus.

Lifileucel (Amtagvi™) is considered medically necessary as a one-time treatment for adults (trials used ≥ 18 years) with unresectable or metastatic cutaneous melanoma, including those with metastatic recurrence, when the following are met:

- Documentation of radiologic disease progression following at least 1 systemic therapy including:
  - A PD-1 blocking antibody **AND**
  - If *BRAF V600* mutation-positive, a BRAF or BRAF/MEK inhibitor
- Documentation of the results of BRAF mutation testing
- Documentation of ≥ 1 resectable lesion (or aggregate of lesions) providing resected tumor tissue ≥ 1.5 cm in diameter to generate Lifileucel **AND**
- ≥ 1 remaining measurable target lesion, as defined by Response Evaluation Criteria in Solid Tumors (RECIST). To view RECIST: The Radiology Assistant : RECIST 1.1 - the basics
- Documentation of Eastern Oncology Cooperative Group (ECOG) performance status ≤ 1.
- Documentation of FEV1 > 60% of predicted. If < 60%, there must be documentation of an evaluation by a pulmonologist.
- Documentation of left ventricular ejection fraction (LVEF) ≥ 45% or New York Heart Association (NYHA) functional classification of Class 1. If LVEF < 45% or NYHA functional classification > Class 1, there must be documentation of an evaluation by a cardiologist.
- Documentation of creatinine clearance (CrCl) ≥ 40mL/min. If < 40mL/min, there must be documentation of an evaluation by a nephrologist.
- No evidence of an active infection.
- Documentation of the following hematologic parameters and appropriate hematologic evaluation:
  - Platelet count ≥ 100,000 cells/mm^3
  - Hemoglobin ≥ 9.0 g/dL
  - Absolute neutrophil count (ANC) ≥ 1000 cells/ mm^3
- Documentation that patient does not have brain metastasis

OR

- If there is evidence of brain metastasis, there is documentation of an appropriate evaluation and treatment to minimize the risk of treatment-related complications such as hemorrhage.
- Patient has no contraindications to high-dose Interleukin-2 (Aldesleukin) therapy based on oncology evaluation.
- Patient has not been previously treated with Lifileucel.
- The medication is prescribed by an oncologist.

After patient selection, the next significant decision is selection of a tumor for TIL harvest. Although tumor size does not correlate with efficacy of TIL therapy, tumors should be at least 2 cm in largest diameter to ensure adequate quantity of tissue for successful processing. Larger tumors may have hypoxic and necrotic centers and do not necessarily yield higher quantities of TIL (Crompton, 2017).

- Tumor resection(s) required to generate adequate quantity of tissue for processing will be considered a medically necessary component of this treatment.

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Appendix

NCCN Categories of Evidence and Consensus

- **Category 1**: The recommendation is based on high-level evidence (i.e., high-powered randomized clinical trials or meta-analyses), and the panel has reached uniform consensus that the recommendation is indicated. In this context, uniform means near unanimous positive support with some possible neutral positions.
- **Category 2A**: The recommendation is based on lower level evidence, but despite the absence of higher level studies, there is uniform consensus that the recommendation is appropriate. Lower level evidence is interpreted broadly and runs the gamut from phase II to large cohort studies to case series to individual practitioner experience. Importantly, in many instances, the retrospective studies are derived from clinical experience of treating large numbers of patients at a member institution, so panel members have first-hand knowledge of the data. Inevitably, some recommendations must address clinical situations for which limited or no data exist. In these instances the congruence of experience-based opinions provides an informed if not confirmed direction for optimizing patient care. These recommendations carry the implicit recognition that they may be superseded as higher level evidence becomes available or as outcomes-based information becomes more prevalent.
- **Category 2B**: The recommendation is based on lower level evidence, and there is nonuniform consensus that the recommendation should be made. In these instances, because the evidence is not conclusive, institutions take different approaches to the management of a particular clinical scenario. This nonuniform consensus does not represent a major disagreement, rather it recognizes that given imperfect information, institutions may adopt different approaches. A Category 2B designation should signal to the user that more than one approach can be inferred from the existing data.
- **Category 3**: The recommendation has engendered a major disagreement among the panel members. Several circumstances can cause major disagreements. For example, if substantial data exists about two interventions but they have never been directly compared in a randomized trial, adherents to one set of data may not accept the interpretation of the other side's results. Another situation resulting in a Category 3 designation is when experts disagree about how trial data can be generalized. A Category 3 designation alerts users to a major interpretation issue in the data and directs them to the manuscript for an explanation of the controversy.

Review and Approval History

Date	Description
02/23/2024	New clinical guideline.
05/08/2024	Approved by Optum Clinical Guideline Advisory Committee.
05/17/2024	Approved by Pharmacy and Therapeutics (P&T) Committee.
06/06/2024	Approved by Medical Technology Assessment Committee (MTAC).
12/04/2025	Annual Review. Approved by Medical Technology Assessment Committee (MTAC).
12/08/2025	Annual Review. Approved by Optum Clinical Guideline Advisory Committee.
12/10/2025	Annual Review. Approved by Medicare Advantage Policy and Technology Assessment Committee (MAP TAC).
12/17/2025	Annual Review. Approved by Pharmacy and Therapeutics (P&T) Committee.