Lifileucel AMTAGVI
National Drug Mini-Monograph
January 2026
VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

Abbreviations: AC, active-controlled; CO, crossover; DB, double-blind; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; MC, multicenter; MN, multinational; PC, placebo-controlled; Q, GRADE quality of evidence; RCT, randomized clinical trial

FDA PRESCRIBING INFORMATION[1]	
Description / MOA	Lifileucel is an autologous tumor-derived T-cell immunotherapy using resected tumor tissue to grow and expand immune cells, especially tumor-infiltrating lymphocytes (TIL), then formulated into a suspension for IV infusion.
Indication Under Review	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 (accelerated approval)
Dosage Regimen	• Lymphodepleting chemotherapy regimen (cyclophosphamide + fludarabine) daily for 7 days before infusion • Pre-medicate 30-60 minutes before infusion: acetaminophen and a H1 antihistamine • A single dose of Lifileucel is divided into 1-4 bags (100-125mL each). Thaw bag(s) and infuse at 1mL/min for 5 minutes, then increase to 5-10mL/min. • 3-24 hours after Lifileucel infusion, administer IL-2 (aldesleukin) at 600,000 IU/kg every 8-12 hours for up to 6 doses in an inpatient unit
Dosage Forms Under Review	Lifileucel suspension for intravenous infusion

EFFICACY CONSIDERATIONS

Trial 1 — **Chesney, et al. C-144-01 Pooled data from Cohorts 2 and 4 from P2 trial[2]**

Design

- Unresectable or metastatic melanoma (Stage IIIC or IV) (Cohorts 2 and 4)
- Disease progression following PD-1 blocking antibody, and if BRAF V600-mutation positive, a BRAF or BRAF/MEK inhibitor
- ECOG 0-1
- Resectable tumor tissue to generate infusion
- Excluded: uveal/ocular melanoma, symptomatic/untreated brain mets, chronic systemic steroids, active systemic infection, chronic heart of lung abnormality (LVEF <45%, FEV1<60%)

Population

- mAge: 56
- Male: 54%
- ECOG 0: 68%
- BRAF mutated: 27%
- Stage IV: 93.5%
- Prior PD-1/PD-L1: 100%
- Prior PD-1 plus anti-CTLA-4: 53.6%
- BRAF ± MEK inhibitor: 25.5%
- Med prior lines of therapy: 3

Intervention

- NMA-LD with cyclophosphamide/fludarabine for 7 days
- Lifileucel infusion
- Abbreviated high-dose IL-2 (aldesleukin): 600,000 IU/kg every 8-12 hours for up to 6 doses

Comparator

None

Results

Cohort 2=66 patients; Cohort 4=87 patients; N=153 patients

Outcome	Pooled
ORR	**31.4%**
mDOR	NR (4.1, NR)
mOS	13.9 mos (95%CI (10.6-17.8)

Authors' Conclusions

- One-time treatment with TIL therapy demonstrates clinically meaningful activity in pre-treated patients with advanced melanoma
- Responses were durable, AEs were transient and manageable.

Trial 2 — **Medina, et al. Long-term efficacy and safety-5-year analysis of c-144-01[3]**

Results

Outcome	Pooled
ORR	**31.4%(CR 5.9%; PR 25.5%)**
	N=4 CR after 1 year
mDOR	36.5 mos (95%CI 8.3-NR)
OS	5-yr OS: 19.7%

Authors' Conclusions

- One-time lifileucel resulted in durable response with 5-year OS of 19.7% in a population with a median of 3 prior systemic therapies.
- Some responses deepened over time; 31.3% of responders completed 5 years of follow-up with ongoing responses
- No new AEs occurred; death due to treatment AEs within or after the first 30 days after lifileucel was 3.2%.

Trial 3

- **Rohaan, et al. Tumor-infiltrating lymphocyte therapy or ipilimumab in advanced melanoma P3[4]**

Population

- mAge:59
- Male: 60%
- BRAF V600 mutation: 43%
- 1L PD-1 monotherapy: 62% (allowed 1 prior line of therapy)

Results

Outcome	Results
mPFS	**7.2 mos vs 3.1 mos; HR 0.50 (95%CI 0.35-0.72)**
ORR	49% (CR 20%) vs 21% (CR 7%)
mOS	25.8 mos vs 18.9 mos. HR 0.83 (95%CI 0.54-1.27)

Authors' Conclusions	• First of second line TIL therapy in advanced melanoma improved PFS more than ipilimumab • 86% of patients received previous PD-1 therapy as either adjuvant or first-line treatment; ORR in this group was 49% vs 20% in the ipilimumab group • Treatment-related adverse events were primarily due to lymphodepleting chemotherapy, IL-2 infusions, or both.
NCCN Guidelines	For patients who progress on 1L therapy, including targeted BRAF therapy, then second or subsequent therapy includes 6 preferred regimens which includes lifileucel
VA Clinical Pathway	• If progression after 1L nivolumab/ipilimumab that is not oligometastatic and tumor is BRAF mutation negative, then provider can choose either lifileucel or nivolumab/relatlimab • If progression after 1L dabrafenib/trametinib that is not oligometastatic and patient is NOT a candidate for dual immunotherapy, then provider can choose either lifileucel or TVEC • If progression after 1L PD-1 inhibitor monotherapy that is not oligometastatic and tumor is BRAF mutation negative, then provider can choose either nivolumab/ipilimumab, nivolumab/relatlimab, lifileucel, or TVEC • If progression after 1L nivolumab/relatlimab that is not oligometastatic and tumor is BRAF mutation negative, the provider can choose either nivolumab/ipilimumab, lifileucel, or TVEC

NMA-LD=non-myeloablative lymphodepletion;

SAFETY CONSIDERATIONS	
Boxed Warnings	Treatment-related mortality, Prolonged severe cytopenia, Severe infection, Cardiopulmonary and Renal impairment
Contraindications	None
Other Warnings	• Treatment-Related Mortality: 7.5% (severe infections, internal hemorrhage, acute renal failure, acute respiratory failure, arrhythmia, ascites, liver injury, bone marrow failure • Prolonged severe cytopenia: 45.5% (g 3 or higher w/o resolution to gr 2 or lasting > 30 days) • Internal Organ Hemorrhage • Severe Infection: 27%; gr3 or higher 13.5%; febrile neutropenia 47% • Cardiac disorders gr3 or higher: 9%; includes tachycardia, atrial fib, arrhythmia, acute MI, cardiac ventricular thrombosis, cardiomyopathy, QT-prolongation • Respiratory failure • Acute renal failure • Hypersensitivity reactions
Top AEs	Chills, pyrexia, fatigue, tachycardia, diarrhea, febrile neutropenia, edema, rash, hypotension, alopecia, infection, hypoxia, dyspnea
Drug Interactions	None
Pregnancy	No data in pregnant women or animal studies; do not administer in women who are pregnant; pregnancy after infusion should be discussed with provider
Lactation	No data on presence in human milk; discuss risks/benefits of breastfeeding and clinical needs of mother for lifileucel

OTHER CONSIDERATIONS	
FDA Review	• The Objective Response Rate and duration of response serve as intermediate endpoints likely to predict clinical benefit in a population with high unmet need. • Overall benefit of lifileucel outweighs the risks in this heavily pre-treated population • Risk mitigation through Boxed Warnings and Precautions • Continue confirmatory trial (IOV-MEL-301) comparing lifileucel plus pembrolizumab vs pembrolizumab alone in newly diagnosed unresectable or metastatic melanoma.

THERAPEUTIC ALTERNATIVES AND THEIR PLACE IN THERAPY

- Subsequent therapy for advanced melanoma is dependent on what was utilized in first-line therapy and subsequent therapies
- First-line therapies are continually evolving and mainly consist of dual immunotherapies but the choice can be tumor-specific or patient comorbidity specific
- Alternative therapies after previous therapy(ies) have not been compared to each other.

DRUG	VANF	CFU	FDA	GUIDELINES
Pembrolizumab 400mg IV Q6 weeks	Yes	Yes	Yes for metastatic melanoma	NCCN VA Clinical Pathway
Talimogene laherparevec (IMLYGIC) (TVEC)	No	No	Yes-unresectable melanoma lesions recurrent after initial surgery	NCCN VA Clinical Pathway
Nivolumab plus ipilimumab	Yes	Yes	Yes for metastatic melanoma	NCCN VA Clinical Pathway
Nivolumab plus relatlimab	No	Yes	Yes for metastatic melanoma	NCCN VA Clinical Pathway
Dabrafenib plus trametinib	Yes	No	Yes for metastatic melanoma with BRAF V600E or V600E mutation	NCCN VA Clinical Pathway

POTENTIAL PLACE IN THERAPY OF ——

1. Lifileucel is a one-time autologous tumor-infiltrating lymphocyte (TIL) therapy approved for unresectable or metastatic melanoma that has progressed on prior PD-1 blockade, and if BRAF V600 mutant, after BRAF ±MEK inhibition. This population may reflect high tumor burden or anti-PD-1 resistance and may have a poor prognosis with limited options for therapy.
2. TIL therapy process consists of 4 phases: 1) Tumor resection and manufacturing of TIL product; 2) Administration of non-myeloablative lymphodepleting chemotherapy generally consisting of 2 days of cyclophosphamide followed by 5 days of fludarabine; 3) Infusion of manufactured TIL product; 4) high-dose IL-2 infusions every 8-12 hours for up to 6 doses.
3. TIL therapy can only be administered at approved Authorized Treatment Centers (ATC). As of January 2026, there are no VAMCs that are ATC approved; veteran patients will need to be referred to an ATC in the community.
4. Efficacy was from pooled cohorts of a single-arm, phase 2 trial of pre-treated patients. The objective response rate of 31% of which 6% were complete responses with a median duration of response of 36.5 months.
5. Toxicity of treatment is not due to the TIL infusion, but is driven by lymphodepletion chemotherapy (thrombocytopenia, anemia, febrile neutropenia) and the high-dose IL-2 (Cytokine Release Syndrome).
6. Candidates for lifileucel (TIL) therapy include: 1. Patients with a targeted tumor for potential resection and harvesting; 2. Willingness to travel to a tertiary treatment center; 3. ECOG Performance Status of 0-1; 4. Adequate hematologic, renal, cardiac (baseline ECHO or MUGA) and pulmonary function; 5. Able to withstand lymphodepleting chemotherapy regimen; 6. Ability to tolerate high-dose IL-2; 7. No rapidly progressing disease, symptomatic or untreated brain metastases, active infection, or significant immunosuppression.
7. Therapeutic alternatives after failure of single-agent anti-PD-1 therapy and BRAF±MEK therapy includes dual immunotherapy (nivolumab + ipilimumab or nivolumab + relatlimab), oncolytic virus therapy with TVEC, and in select cases single-agent chemotherapy.

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References

1 Amtagvi (lifileucel) suspension for intravenous infusion; Philadelphia, PA: Iovance Biotherapeutics Manufacturing LLC. Februrary 2024.

2 Chesney J, Lewis KD, Kluger H, et al. Efficacy and safety of lifileucel, a one-time autologous tumor-infiltrating lymphocyte (TIL) cell therapy, in patients with advanced melanoma after progression in immune checkpoint inhibitors and targeted therapies: pooled analysis of consecutive cohorts of the C-144-01 study. J ImmunoTherapy of Cancer 2022; 10: e005755. doi:10.1136/jitc-2022-005755.

3 Medina T, Chesney JA, Kluger HM, et al. Long-term efficacy and safety of lifileucel tumor-infiltrating lymphocyte cell therapy in patients with advanced melanoma: a 5-year analysis of the C-144-01 study. J Clin Oncol 2025; 43:3565-3572. DOI https://doi.org/10.1200/JCO-25-00765

4 Rohaan MW, Borch TH, van den Berg JH, et al. Tumor-infiltrating lymphocyte therapy or ipilimumab in advanced melanoma. New Eng J Med 2022: 387: 2113-25. DOI: 10.1056/NEJMoa2210233