Patient Selection Criteria and Surgical Resection Considerations for AMTAGVI™ (lifileucel)

Considerations when evaluating patients with previously-treated advanced melanoma

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).

Patient Selection Criteria

- ❑ Diagnosis of unresectable or metastatic melanoma
- ❑ Treated with a prior PD-1 blocking antibody, and if BRAF mutation positive, a BRAF +/-MEK inhibitor[1]

Additional Considerations for AMTAGVI*

- ECOG performance status of 0-1
- Slow to moderate speed of disease progression
- Overall physical fitness, including appropriateness to undergo lymphodepletion (LD) and IL-2, as part of a cell therapy regimen
- Study excluded patients with uncontrolled brain metastases

WARNING: TREATMENT-RELATED MORTALITY, PROLONGED SEVERE CYTOPENIA, SEVERE INFECTION, CARDIOPULMONARY and RENAL IMPAIRMENT

- Monitor patients for prolonged severe cytopenia and monitor for internal organ hemorrhage
- Administer filgrastim or a biosimilar product to patients beginning Day 1 after AMTAGVI and continuing daily until the absolute neutrophil count (ANC) is greater than 1000 per mm^3 for 3 consecutive days, or per institutional standard
- Treat severe infections
- Monitor cardiopulmonary and renal functions throughout the treatment course

Administer in an inpatient hospital setting. An intensive care facility and specialists skilled in cardiopulmonary or intensive care medicine must be available.

Please refer to full prescribing information for additional information on AMTAGVI (lifileucel)

*Select eligibility criteria from C-144-01 study[2]

Surgical Resection Considerations

 **Amount of Viable Tumor Tissue Needed**	To generate lifileucel, at least one resectable lesion (or aggregate of lesions) with a minimum of 1.5 cm diameter up to 4 cm diameter is required. If the selected lesion is not at least 1.5 cm in diameter, other lesions can be added up to 4 cm in diameter total.[1]
 **Tumor Site Selection**	Lifileucel can be manufactured regardless of anatomic surgery site. Lesion origin of AMTAGVI products in the C-144-01 trial were skin, lymph nodes, liver, lung, peritoneal, musculoskeletal, breast, and other anatomic sites including chest wall, abdominal wall, adrenal gland, abdominal-peritoneal, paraesophageal, axillary, thigh, back, supraclavicular, and soft tissue.[1] When possible, nonvisceral lesions should be considered over visceral lesions. During surgery, consider selecting zones within the resected lesion that are more likely to be highly infiltrated with T cells.[3]
 **Minimizing Contamination**	Tumor tissue should be procured in an aseptic environment, targeting anatomic site(s) of low/minimum bioburden when possible.[3] Every effort should be made to keep tumor tissue free from contamination.
 **Recommendations for Prosection**	Transport media must be prepped in advance in an OR under a hood with aseptic conditions. Promptly transfer tumor tissue to a sterile surface in the OR/surgical suite for immediate processing. Trim the tumor tissue to remove extraneous non-tumor tissue; care should be taken to exclude hemorrhagic, fibrotic, and necrotic tissue.[3]

Please see next page for addtional Important Safety Information

Important Safety Information (continued)

Treatment-Related Mortality
AMTAGVI is associated with treatment-related mortality. In the clinical trial, the treatment-related mortality rate was 7.5% (N=160), including 2 deaths during the lymphodepleting period, 6 deaths within 30 days, and 4 deaths 38 to 150 days following AMTAGVI administration. Adverse reactions associated with these deaths included severe infections (sepsis, pneumonia and encephalitis), internal organ hemorrhage (abdominal hemorrhage and intracranial hemorrhage), acute renal failure, acute respiratory failure, cardiac arrythmia, extensive ascites and liver injury and bone marrow failure. Because clinical trials are conducted under widely varying conditions, treatment-related mortality rates observed in the clinical trials of a drug may not reflect the rates observed in practice.

Prolonged Severe Cytopenia
Patients treated with AMTAGVI may exhibit Grade 3 or higher cytopenia for weeks or longer. Based on adverse event reporting, Grade ≥ 3 cytopenia or pancytopenia which did not resolve to ≤ Grade 2 or lasted beyond 30 days post AMTAGVI infusion occurred in 45.5% of melanoma patients who received AMTAGVI. Prolonged cytopenia included thrombocytopenia (30.1%), lymphopenia (19.9%), neutropenia (17.3%), leukopenia (14.7%) and pancytopenia (1.3%). Monitor blood counts after AMTAGVI infusion.

Internal Organ Hemorrhage
Patients treated with AMTAGVI may exhibit internal organ hemorrhage. Intraabdominal and intracranial hemorrhage can be life-threatening and has been associated with at least two deaths in patients who received AMTAGVI. Withhold or discontinue AMTAGVI infusion if internal organ hemorrhage is indicated, or if patient is deemed ineligible for IL-2 (aldesleukin) infusion. Patients with persistent or repeated thrombocytopenia after receiving AMTAGVI should not use anticoagulant(s) or must be under close monitoring if the patient must take an anticoagulant.

Severe Infection
Severe, life-threatening, or fatal infections occurred in patients after AMTAGVI infusion. Treatment-related infections (any severity) occurred in 26.9% of melanoma patients. Grade 3 or higher infections occurred in 13.5% of patients, including 10.9% of patients with infections of an unspecified pathogen and 3.8% of patients with infections of a specified pathogen. Do not administer AMTAGVI to patients with clinically significant systemic infections. Monitor patients for signs and symptoms of infection before and after AMTAGVI infusion and treat appropriately. Administer prophylactic antimicrobials according to institutional guidelines. Febrile neutropenia was observed in 46.8% of melanoma patients after AMTAGVI infusion. In the event of febrile neutropenia, evaluate for infection and manage with broad-spectrum antibiotics, fluids, and other supportive care as medically indicated.

Cardiac Disorder
Patients treated with AMTAGVI may exhibit cardiac disorder. Grade ≥ 3 cardiac disorders related to the AMTAGVI regimen occurred in 9.0% (14/156) of patients who received AMTAGVI including tachycardia, atrial fibrillation, arrhythmia, acute myocardial infarction, cardiac ventricular thrombosis, cardiomyopathy, QT-prolongation. Cardiac arrhythmia resulted in one death among melanoma patients who received AMTAGVI. Monitor patients with signs and symptoms of cardiac disorder before and after AMTAGVI infusion. Withhold or discontinue AMTAGVI if severe cardiac disorder is indicated, or if patient is deemed ineligible for IL-2 (aldesleukin) infusion.

Respiratory Failure
Patients treated with AMTAGVI may develop worsened respiratory function which has been associated with deaths. Monitor patients with signs and symptoms of respiratory failure before and after AMTAGVI infusion. Withhold or discontinue AMTAGVI infusion if severe acute respiratory failure is indicated, or if patient is deemed ineligible for IL-2 (aldesleukin) infusion.

Acute Renal Failure
Patients treated with AMTAGVI may develop worsened renal function which has been associated with deaths. Monitor patients with signs and symptoms of acute renal failure before and after AMTAGVI infusion. Withhold or discontinue AMTAGVI if severe acute renal injury is indicated, or if patient is deemed ineligible for IL-2 (aldesleukin) infusion.

Hypersensitivity Reactions
Allergic reactions, including serious hypersensitivity (e.g. anaphylaxis), may occur with the infusion of AMTAGVI. Acute infusion reactions (within 1 day of infusion) may include fever, rigors or chills, tachycardia, rash, hypotension, dyspnea, cough, chest tightness, and wheezing. These events generally resolve on the same day of infusion. Monitor patients during and after infusion for signs and symptoms of a severe reaction and treat promptly.

Adverse Reactions
The most common (incidence of ≥ 20%) non-laboratory adverse reactions were chills, pyrexia, fatigue, tachycardia, diarrhea, febrile neutropenia, edema, rash, hypotension, alopecia, infection, hypoxia, and dyspnea. The most common Grade 3 or 4 laboratory abnormalities (incidence of at least 10%) were thrombocytopenia, neutropenia, anemia, leukopenia, lymphopenia, and hypophosphatemia. Other adverse reactions that occurred in < 10% of patients included eye disorders, immune system disorders (infusion-related reactions, anaphylactic reaction, cytokine release syndrome), and vitiligo.

You may report side effects to Iovance at 1-833-400-4682, or to the FDA, at 1-800-FDA-1088 or at www.fda.gov/medwatch.

Please see accompanying Full Prescribing Information, including BOXED WARNINGS, for additional Important Safety Information.

References:

1. AMTAGVI [package insert] Iovance Biotherapeutics Inc, 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 on immune checkpoint inhibitors and targeted therapies: pooled analysis of consecutive cohorts of the C-144-01 study. *J Immunother Cancer*. 2022;10(12):e005755.
3. Mullinax JE, Egger ME, McCarter M, et al. Surgical Considerations for Tumor Tissue Procurement to Obtain Tumor-Infiltrating Lymphocytes for Adoptive Cell Therapy. *Cancer J*. 2022 Jul-Aug 01;28(4):285-293.

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