PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]AMTAGVI™

lifileucel

Cell suspension of 7.5 x 10^9 to 72 x 10^9 viable cells for intravenous infusion

100 mL of lifileucel per bag (1 to 4 patient-specific bags per dose)

Antineoplastic agents, Antineoplastic cell and gene therapy

"AMTAGVI, indicated for:

- the treatment of adult patients with unresectable or metastatic melanoma that has progressed on or after at least one prior systemic therapy including a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor, and who have no satisfactory alternative treatment options.

was issued market authorisation with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorisation. For further information for AMTAGVI please refer to Health Canada's Notice of Compliance with conditions - drug products web site"

Iovance Biotherapeutics, Inc.

825 Industrial Rd Fl 1

San Carlos, CA 94070

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Distributed by: Bioscript Logistics Inc.

5-3278 South Service Road West

Oakville, Ontario, Canada L6L 0B1

Submission Control Number: 293019

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorised under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

Table of Contents

Certain sections or subsections that are not applicable at the time of the most recent authorised product monograph are not listed.

Part 1: Healthcare Professional Information

1 Indications

AMTAGVI™ (lifileucel) is a tumour-derived autologous T-cell immunotherapy indicated for:

- the treatment of adult patients with unresectable or metastatic melanoma that has progressed on or after at least one prior systemic therapy including a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor, and who have no satisfactory alternative treatment options.

The marketing authorisation with conditions is primarily based on tumour objective response rate and durability of response. An improvement in survival has not yet been established (see 14 Clinical Trials).

1.1 Paediatrics

Paediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorised an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): No clinically important differences in effectiveness were observed between patients aged 65 years and older compared to patients overall. Limited information is available to draw conclusions on any differences in safety between younger and elderly patients (see 7 Warnings and Precautions, 7.1.4 Geriatrics).

2 Contraindications

- AMTAGVI is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition and Packaging.

3 Serious Warnings and Precautions Box

Severe and fatal adverse reactions have occurred in patients treated with the AMTAGVI regimen, including:

- Prolonged severe cytopenia and severe infections (see 4 Dosage and Administration, 7 Warnings and Precautions and 8 Adverse Reactions).
- Internal organ hemorrhage (see 7 Warnings and Precautions and 8 Adverse Reactions).
- Cardiopulmonary impairment (see 7 Warnings and Precautions and 8 Adverse Reactions).
- Renal impairment (see 7 Warnings and Precautions and 8 Adverse Reactions).

AMTAGVI is administered as a one-time treatment in an inpatient hospital setting at a qualified treatment center under the supervision of a physician experienced in the use of anti-cancer agents.

4 Dosage and Administration

4.1 Dosing Considerations

AMTAGVI is for autologous and intravenous use only.

Verify the patient's identity prior to infusion.

Administer at a qualified healthcare facility.

4.2 Recommended Dose and Dosage Adjustment

- AMTAGVI is provided as a single dose for infusion containing a suspension of tumour-derived T cells. The dose is supplied in 1 to 4 patient-specific IV infusion bag(s) in individual protective metal cassettes. Each dose contains 7.5 x 10^9 to 72 x 10^9 viable cells.
- Health Canada has not authorised an indication for paediatric use.

4.4 Administration

AMTAGVI is for autologous use only.

The patient's identity must match the patient identifiers on the AMTAGVI cassette(s) and infusion bag(s).

Preparing Patient for AMTAGVI Infusion

Confirm availability of AMTAGVI and IL-2 (aldesleukin) prior to starting the lymphodepleting regimen.

Pretreatment

Administer a lymphodepleting chemotherapy regimen of cyclophosphamide 60 mg/kg intravenously with mesna daily for 2 days followed by fludarabine 25 mg/m^2 intravenously daily for 5 days before infusion of AMTAGVI. See the product monographs for lymphodepleting chemotherapy for information on dose modifications.

Infuse AMTAGVI as soon as possible after 24 hours have elapsed following the last dose of fludarabine, but no later than 4 days.

Administer broad spectrum antibiotics if fever is present and absolute neutrophil count (ANC) is less than 0.5 x 10^9/L, or per institutional standard.

Premedication

Pre-medicate the patient with acetaminophen and diphenhydramine or another H1-antihistamine, approximately 30 to 60 minutes prior to AMTAGVI infusion.

Avoid prophylactic use of systemic corticosteroids which may interfere with the activity of AMTAGVI.

Receipt of AMTAGVI

AMTAGVI is shipped directly to the treatment centre in the vapour phase of a liquid nitrogen cryoshipper. All treatment centers should have onsite storage in vapour phase of liquid nitrogen.

Product and patient-specific labels are located on both the product infusion bag(s) and protective metal cassette(s), which are inside the liquid nitrogen cryoshipper.

- Match the identity of the patient with the patient identifiers on the cassette(s) and infusion bag(s) upon receipt.

- Confirm the number of AMTAGVI cassette(s) and infusion bag(s) matches the total number of cassettes and infusion bags on the shipment packing slip.
- Store AMTAGVI frozen in the vapour phase of liquid nitrogen (less than or equal to minus 150°C).

Administration of AMTAGVI

The AMTAGVI dose is contained in 1 to 4 cryopreserved patient-specific infusion bag(s) in individual protective metal cassette(s). Thaw and infuse 1 bag at a time if more than 1 bag has been provided. Wait to thaw the next bag until the previous bag has been safely and completely administered.

Preparation of AMTAGVI

Do not thaw the product until the patient is ready to be infused. Coordinate the timing of AMTAGVI thaw and infusion. Confirm the infusion time in advance and adjust the start time for thaw so that AMTAGVI is available for infusion when the patient is ready. Once 1 bag of AMTAGVI is thawed, the infusion should be started as soon as possible and must be completed within 3 hours at room or ambient temperature (18°C to 25°C).

1. Confirm the availability of IL-2 (aldesleukin).
2. Prior to AMTAGVI preparation, match the recipient's identity with the patient identifiers on the AMTAGVI cassette label. Do not remove the AMTAGVI infusion bag from the cassette if the patient identifiers on the AMTAGVI cassette label do not match the intended patient. Contact Iovance Biotherapeutics, Inc. at 1-833-215-7566 if there are any discrepancies.
3. Once recipient identification on the cassette is confirmed, remove the AMTAGVI infusion bag from the cassette. Check that the patient identifiers on the cassette label match the patient identifiers on the AMTAGVI infusion bag label and match the recipient's identity with the patient identifiers on the AMTAGVI infusion bag label. Contact Iovance Biotherapeutics, Inc. at 1-833-215-7566 if there are any discrepancies.
4. Inspect each bag for any breaks or cracks prior to thawing. Inspect the spike ports for any damage prior to thawing. If a bag is damaged or compromised, do not infuse the contents and contact Iovance Biotherapeutics, Inc. at 1-833-215-7566.
5. For thawing, place the infusion bag inside a second sealable bag (preferably sterile) per local guidelines in case of a leak and to protect ports from contamination.
6. Thaw AMTAGVI at approximately 35°C to 39°C using either a water bath or a dry thaw method until there is no visible ice or frozen contents in the infusion bag. Total time from start of thaw until completion of thawing should be no more than 10 minutes.
7. Immediately remove bag from thawing device. Remove the infusion bag from the sealable plastic bag and wipe dry. Do not wash, spin down, or resuspend AMTAGVI in new media prior to infusion.
8. Once thawed, inspect the contents of the thawed infusion bag. If cell agglomerates are visible, gently mix the contents of the bag by inverting the bag prior to infusion. If needed, gently massage the bag to disperse cell agglomerates. Do not infuse the contents of an infusion bag if it is damaged or leaking, or otherwise appears to be compromised.
9. Administer each bag of AMTAGVI as soon as possible. If needed, AMTAGVI may be maintained at room temperature (18°C to 25°C) not to exceed 3 hours. Do not re-freeze or refrigerate thawed

product.

Infusion of AMTAGVI

10. Before infusion, the patient's health status should be reassessed and confirmed to be acceptable prior to AMTAGVI and IL-2 administration.
11. Confirm the patient's identity matches with the patient identifiers on the infusion bag.
12. A Y-type blood filter with a pore size in the range of 150-260 microns is required. Do NOT use a leukocyte depleting filter with AMTAGVI.
13. Prime the tubing with normal saline prior to infusion.
14. Initiate the infusion. Infuse the entire contents of each bag as soon as possible but within 3 hours of thawing.
15. Administer AMTAGVI at an infusion rate of approximately 1 mL per minute for the initial 5 minutes, thereafter 5 mL to 10 mL per minute.
16. Contents of all bags must be infused to complete a single dose. After the last bag is infused, rinse the tubing with normal saline at the same infusion rate to ensure all product is delivered.
17. Monitor patient during and after infusion (see 7 Warnings and Precautions and 8 Adverse Reactions).

AMTAGVI contains human cells. Follow universal and local biosafety guidelines applicable for the handling and disposal of AMTAGVI to avoid potential transmission of infectious diseases.

Administration of IL-2 (aldesleukin)

Beginning 3 to 24 hours after AMTAGVI infusion, administer intravenous IL-2 (aldesleukin) at 600,000 IU/kg every 8 to 12 hours for up to a maximum of 6 doses to support cell expansion in vivo. The optimal number of aldesleukin doses is different for each individual patient and should be guided by tolerance. Doses should be held for toxicities as per the aldesleukin product monograph. Decisions to restart aldesleukin after toxicity should be based on the reversibility and severity of the toxicity leading to the initial hold and meeting the criteria to restart aldesleukin in the product monograph.

IL-2 (aldesleukin) should be administered in a qualified treatment centre under the supervision of a physician experienced in the use of anticancer agents. See the product monograph IL-2 (aldesleukin) for information on patient selection, patient monitoring and adverse reactions.

Infection prophylaxis after AMTAGVI administration

Administer filgrastim (5 mcg/Kg/day) or a biosimilar product to patients beginning Day 1 after AMTAGVI and continue daily until the ANC is greater than 1×10^9/L for 3 consecutive days, or per institutional standard.

Administer antifungals on Day 1 after AMTAGVI and continue daily until the ANC is greater than 1×10^9/L, or per institutional standard.

Administer Pneumocystis jirovecii pneumonia prophylaxis beginning on Day 14 and continuing for at least 6 months or until ALC count > 1×10^9/L and CD4 count is > 0.2×10^9/L, or per institutional standard.

Administer Herpes simplex virus (HSV) prophylaxis beginning on Day 14 or as deemed appropriate and continuing for at least 6 months until ALC count > 1 x 10^9/L and CD4 count is > 0.2 x 10^9/L.

5 Overdose

Not applicable

6 Dosage Forms, Strengths, Composition and Packaging

Table 1 – Dosage Forms, Strengths and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous infusion	Cell suspension for intravenous infusion. A single dose contains 7.5 x 10^9 to 72 x 10^9 viable cells suspended in a cryopreservation medium. A single dose is split into 1 to 4 patient-specific infusion bag(s) (100 mL per bag) in individual protective metal cassettes	cryopreserved in 5% DMSO, 0.5% albumin (human), and 300 IU/mL IL-2 (aldesleukin). May contain trace amounts of gentamicin, streptomycin, and amphotericin B

7 Warnings and Precautions

Please see 3 Serious Warnings and Precautions Box

General

AMTAGVI should be administered in a qualified treatment centre with personnel trained in handling and administering AMTAGVI and in the management of patients treated with AMTAGVI, including monitoring and managing cytokine release syndrome, capillary leak syndrome, and neurologic adverse reactions. The facility should have immediate access to appropriate emergency equipment and intensive care unit.

AMTAGVI is intended solely for autologous use and should under no circumstances be administered to other patients. Before infusion, the patient's identity must match the patient identifiers on the AMTAGVI infusion bag and cassette. Do not infuse AMTAGVI if the information on the patient-specific label does not match the intended patient (see 4 Dosage and Administration).

Due to the risks associated with the AMTAGVI regimen, consider delaying or foregoing lymphodepleting chemotherapy, AMTAGVI, and aldesleukin treatment if the patient has one or more of the following conditions: clinically significant cardiac dysfunction, pulmonary dysfunction, renal dysfunction, or hepatic dysfunction; clinically significant active uncontrolled infection; or serious active hemorrhage.

When considering patients for treatment with the AMTAGVI regimen, physicians should assess the impact of rapidly progressing disease on the ability of patients to receive the AMTAGVI infusion. Some patients may not benefit from AMTAGVI treatment due to the potential for an increased risk of early death if the disease progresses rapidly.

Educational material for healthcare professionals and patients related to the risks of capillary leak syndrome, cytokine release syndrome, and neurologic toxicity including immune effector cell-associated

neurotoxicity syndrome are available via the Learning Management System.

Treatment-Related Mortality

The AMTAGVI regimen (lymphodepletion, AMTGAVI infusion, and IL-2 aldesleukin) 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. See section 8.1 Adverse Reaction Overview for Adverse Reactions causing these deaths. 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.

Cardiovascular

Cardiac Disorder

Severe cardiac disorders, including life-threatening or fatal reactions, have occurred in patients after receiving the AMTAGVI regimen. Serious cardiac disorders included acute myocardial infarction, arrhythmia, and atrial fibrillation. Cardiac arrhythmia resulted in one death among melanoma patients who received the AMTAGVI regimen.

Patients should be monitored for signs and symptoms of cardiac disorder before and after administration of the AMTAGVI regimen. If there is evidence of significant cardiac dysfunction, or patient is deemed ineligible for aldesleukin, withhold or discontinue the AMTAGVI regimen.

Capillary Leak Syndrome

Capillary leak syndrome, which was sometimes severe, occurred following treatment with the AMTAGVI regimen. The median time to onset following AMTAGVI infusion was 3.5 days (range: 1 to 13 days). Capillary leak syndrome can occur secondary to the administration of aldesleukin as part of the AMTAGVI regimen, is characterised by hypotension, dyspnoea, oedema, and hypoalbuminemia, and can result in end organ toxicity including cardiac, respiratory, renal, and hepatic toxicity.

Aldesleukin should not be administered to patients with significant cardiac, pulmonary, renal, or hepatic impairment. Use of aldesleukin should be avoided with other products known to cause hypotension including antihypertensive drugs, those that cause renal toxicity, or hepatotoxicity.

Capillary leak syndrome may begin immediately after aldesleukin treatment is initiated. Patients should be monitored for signs and symptoms of capillary leak syndrome including assessments of vital signs, weight, fluid intake, albumin levels and urine output.

Aldesleukin should be withheld or discontinued for failure to maintain organ perfusion as demonstrated by altered mental status, reduced urine output, oxygen saturation <90 %, a fall in the systolic blood pressure below 90 mm Hg, or onset of cardiac arrhythmias. If capillary leak is suspected, standard management for capillary leak syndrome should be initiated, which may include intensive care.

Driving and Operating Machinery

The AMTAGVI treatment regimen has a major influence on the ability to drive and use machines. Encephalopathy, delirium, depressed level of consciousness, dizziness, tiredness, and weakness are possible side effects. Due to the potential for events that may impact the patient's ability to drive and use machines, patients should refrain from driving or operating heavy or potentially dangerous machines for at least 3 weeks after infusion.

Hematologic

Prolonged Cytopenia

Patients may exhibit serious or prolonged cytopenia following lymphodepleting chemotherapy and the AMTAGVI infusion.

Grade 3 or higher cytopenia (based on laboratory values), which did not resolve to less than or equal to Grade 2 within 30 days of the AMTAGVI infusion, was observed in 24 (15.4%) patients and included Lymphopenia (13.5%), Anaemia (3.5%), Thrombocytopenia (3.4%), Neutropenia (1.9%), and Leukopenia (1.9%).

Blood counts should be monitored prior to and after the AMTAGVI infusion. Cytopenias should be managed according to institutional guidelines (i.e. use of filgrastim for neutropenia or transfusion support).

Internal Organ Hemorrhage

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

Immune

Severe Infection

Severe, life-threatening, or fatal infections, including opportunistic infections, occurred in patients after AMTAGVI infusion.

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 41.7% of patients with melanoma 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.

Cytokine Release Syndrome

Cytokine release syndrome has occurred following administration of the AMTAGVI regimen. In clinical studies, the median time to onset of CRS following AMTAGVI infusion, any grade, was 3 days (range: 1 to 10 days).

Monitoring and management of cytokine release syndrome

Cytokine release syndrome should be identified based on clinical presentation. Patients should be evaluated for other causes of fever, hypoxia, and hypotension, including capillary leak syndrome, sepsis, tumour progression, heart failure, thromboembolism, and allergic reaction.

Patients should be monitored for the first 4 days following the lifileucel infusion at the qualified treatment centre for signs and symptoms of cytokine release syndrome. After the first 4 days following infusion, the patient should be monitored at the physician's discretion.

Mild cytokine release syndrome can often be managed with supportive care, such as fluids and

antipyretics. Severe cytokine release syndrome may require aggressive interventions, including corticosteroids and anti-cytokine medications like tocilizumab.

Monitoring and Laboratory Tests

Monitor patients at the qualified treatment centre following infusion of AMTAGVI and aldesleukin for signs of potential capillary leak syndrome, neurologic events, cytokine release syndrome, and other toxicities. Consider monitoring of hematological, renal function and other laboratory parameters depending on observed toxicities and recovery. Monitor cardiopulmonary functions. Patients may be discharged from the treatment centre at the physician's discretion once the patient has been deemed to be recovered from the acute effects of IL-2 (aldesleukin).

CRS and neurologic adverse reactions can occur after the infusion of the AMTAGVI regimen. Instruct patients to remain within proximity of the qualified treatment centre after completing infusion of the AMTAGVI regimen, at the physician's discretion.

Educate patients and their caregivers on the signs and symptoms of CRS, capillary leak syndrome, and neurologic adverse reactions. Advise patients and their caregivers to immediately contact the designated health professional if CRS, capillary leak syndrome, or neurologic adverse reactions are suspected.

Neurologic

Neurological toxicities, such as mental status changes, speech difficulties, cortical blindness, limb or gait ataxia, hallucinations, agitation, obtundation, demyelinating polyneuropathy, coma and immune effector cell-associated neurotoxicity syndrome (ICANS), which were sometimes severe, can occur following treatment with the AMTAGVI regimen. The median time to onset of serious neurological adverse reactions following AMTAGVI infusion was 10.5 days (range: 4 to125).

Patients should be monitored for signs and symptoms of neurological toxicity during treatment with the AMTAGVI regimen. Aldesleukin should be discontinued in patients developing moderate to severe lethargy or somnolence, coma or toxic psychosis or for repetitive or difficult to control seizures.

Central nervous system metastases should be evaluated and treated prior to initiation of the AMTAGVI regimen. If possible, concomitant use of the AMTAGVI regimen with other products with a known potential to cause neurotoxicity, or use of the AMTAGVI regimen in patients with seizure disorders or abnormal intracranial imaging should be avoided.

Renal

Acute Renal Failure

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

Reproductive Health

- Fertility

There are no data on the effects of AMTAGVI on fertility. Effects of AMTAGVI on male and female fertility have not been evaluated in animal studies.

Respiratory

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 the AMTAGVI infusion. Withhold or discontinue the AMTAGVI regimen if severe acute respiratory failure is indicated, or the patient is deemed ineligible for IL-2 (aldesleukin) infusion.

Sensitivity/Resistance

Hypersensitivity Reactions

Allergic reactions including serious hypersensitivity (e.g., anaphylaxis) may occur with the infusion of AMTAGVI.

Acute infusion reactions (defined as occurring within 1 day of infusion) may occur and include fever, rigors or chills, tachycardia, rash, hypotension, dyspnea, cough, chest tightness, and wheezing. These events generally resolve on the same day of infusion. Patients should be monitored during and after infusion for signs and symptoms of a severe reaction, and treated promptly.

7.1 Special Populations

7.1.1 Pregnant Women

There are no available data with AMTAGVI use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with AMTAGVI. Therefore, AMTAGVI is not recommended for women who are pregnant, and pregnancy after AMTAGVI administration should be discussed with the treating physician. Report pregnancies to Iovance Biotherapeutics, Inc. at 1-833-215-7566.

Pregnancy testing

Pregnancy status for females of child-bearing age should be verified prior to starting treatment with AMTAGVI.

Contraception

Patients of childbearing potential or their partners of childbearing potential must be willing to take the appropriate precaution to avoid pregnancy or fathering a child for the duration of the treatment and practice an approved, highly effective method of birth control for 12 months after receiving the AMTAGVI regimen. See the product monographs for lymphodepleting chemotherapy and IL-2 (aldesleukin) for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy and aldesleukin.

7.1.2 Breastfeeding

There is no information regarding the presence of AMTAGVI in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AMTAGVI and any potential adverse effects on the breastfed infant from AMTAGVI or from the underlying maternal condition.

7.1.3 Paediatrics

Paediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorised an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): Of 156 patients with unresectable or metastatic melanoma who were treated with AMTAGVI in clinical studies, 37 patients (23.7%) were 65 years of age or older. Limited information is available to draw conclusions on any differences in safety between younger and elderly patients. No clinically important differences in effectiveness were observed between patients aged 65 years and older compared to patients overall.

8 Adverse Reactions

8.1 Adverse Reaction Overview

Unresectable or metastatic melanoma that has progressed on or after a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor, and who have no satisfactory alternative treatment options

The safety data described in this section reflect exposure to AMTAGVI within a regimen that included cyclophosphamide, fludarabine, and IL-2 (aldesleukin) in Study C-144-01, an open-label, multicenter, multicohort, single-arm study in which 156 adult patients with unresectable or metastatic melanoma received a single infusion of AMTAGVI. The median AMTAGVI administered dose was 20.9×10^9 viable cells (min, max: 0.4×10^9, 99.5×10^9). The median age of the study population was 56 years (range: 20 to 79 years); 53.8% were men. The performance status prior to tumour procurement was 68.6% with ECOG 0 and 31.4% with ECOG 1.

The most common (incidence of ≥ 30%) non-laboratory adverse reactions were chills (75.0%), pyrexia (53.2%), fatigue (48.1%), arrhythmia (47.4%), oedema (45.5%), rash (44.2%), febrile neutropenia (41.7%), hypotension (35.9%), dyspnoea (34.6%), and diarrhoea (32.1%).

The most common (incidence of ≥ 5%) Grade 3 non-laboratory adverse reactions were febrile neutropenia (41.7%), infection – pathogen unspecified (12.2%), rash (11.5%), hypotension (10.9%), hypoxia (10.9%), pyrexia (10.9%), hypertension (9.0%), fatigue (7.7%), infection - bacterial (7.1%), dyspnoea (6.4%), encephalopathy (6.4%), acute kidney injury (5.1%), arrhythmia (5.1%) and chills (5.1%).

The most common (incidence of ≥ 1%) Grade 4 non-laboratory adverse reactions were sepsis (4.5%), acute kidney injury (2.6%), respiratory failure (1.9%), edema (1.9%), hemorrhage (1.3%), hypotension (1.3%), hypoxia (1.3%) and pancytopenia (1.3%).

The most common (incidence of ≥ 2%) serious non-laboratory adverse reactions were infections – pathogen unspecified (7.7%), sepsis (5.1%), febrile neutropenia (5.1%), haemorrhage (4.5%), acute kidney injury (3.8%), dyspnoea (3.8%), encephalopathy (3.2%), edema (3.2%), infections – viral (2.6%), respiratory failure (2.6%) and pyrexia (2.6%).

There were 10 deaths (6.4%) that were at least possibly related to the treatment, including 6 deaths within 30 days following AMTAGVI administration and 4 deaths between 35 days and 150 days following AMTAGVI administration. They were sepsis, pneumonia, encephalitis, intra-abdominal hemorrhage, intracranial hemorrhage, cardiac arrhythmia, acute respiratory failure, renal failure, ascites and liver injury, and bone marrow failure. Among the 160 patients who initiated the lymphodepleting

chemotherapy regimen, 2 treatment-related deaths occurred during the lymphodepleting period. They were septic shock and acute kidney injury.

Additional Information on Selected Adverse Reactions:

The selected adverse reactions described below are based on the 156 patients from the Study C-144-01, who had unresectable or metastatic melanoma and who had received a single dose of AMTAGVI infusion.

Prolonged Severe Cytopenia

In Study C-144-01 (N=156), Grade 3 or higher cytopenias that had not resolved to Grade 2 or lower by Day 30 following the AMTAGVI infusion included lymphopenia (13.5%), anemia (3.5%), thrombocytopenia (3.4%), leukopenia (1.9%), and neutropenia (1.9%).

Table 2 lists the incidences of Grade 3 or higher cytopenias occurring after dosing that had not resolved to Grade 2 or lower by Day 30, based on laboratory data.

Table 2 – Incidences of Prolonged Cytopenias Following Treatment with AMTAGVI in Study C-144-01

N = 156	Neutropenia n(%)	Leukopenia n(%)	Lymphopenia n(%)	Thrombocytopenia n(%)	Anemia n(%)
Frequency of G3 or higher events within 30 days post Amtagvi infusion	156 (100)	156 (100)	156 (100)	147 (94.2)	113 (72.4)
Initial Grade 3/4 Not Recovered to ≤Grade 2 by Day 30	3 (1.9)	3 (1.9)	21 (13.5)	5 (3.4)	4 (3.5)

Internal Organ Haemorrhage

Haemorrhage occurred in 33 patients (21.2%) in the C-144-01 study; 4 (2.6%) experienced Grade 3 and 2 (1.3%) experienced Grade 4 haemorrhage, and fatal haemorrhage occurred in 3 patients (1.9%) and included cerebral haemorrhage, intra-abdominal haemorrhage, and intracranial haemorrhage. See 7 Warnings and Precautions for monitoring and management guidance.

Severe Infections

Infections occurred in 72 patients (46.2%) in the C-144-01 study; 25 (16.0%) experienced Grade 3 and 8 (5.1%) experienced Grade 4 infections, and fatal infections occurred in 3 patients (1.9%). Infections that were ≥ Grade 3 included pneumonia, urinary tract infection, bacteremia, rash pustular, device-related infection, meningitis, skin infection, encephalitis, endocarditis, gallbladder abscess, infections - bacterial, infections - viral, sepsis, infections - fungal, and tuberculosis.

Febrile neutropenia was observed in 41.7% of patients with 5.1% experiencing serious febrile neutropenia. See 7 Warnings and Precautions for monitoring and management guidance.

Cardiac Disorders

Cardiac disorders occurred in 76 patients (48.7%) in the C-144-01 study; 8 (5.1%) experienced Grade 3 and 2 (1.3%) experienced Grade 4 cardiac disorders, and fatal cardiac disorders occurred in 1 patient

(0.6%). Cardiac disorder that were ≥ Grade 3 included arrhythmia and acute myocardial infarction. See 7 Warnings and Precautions for monitoring and management guidance.

Respiratory Failure

Respiratory failure or acute respiratory failure occurred in 7 patients (4.5%) in the C-144-01 study; 1 (0.6%) experienced Grade 3 and 3 (1.9%) experienced Grade 4 respiratory failure or acute respiratory failure, and fatal respiratory failure or acute respiratory failure occurred in 1 patient (0.6%). See 7 Warnings and Precautions for monitoring and management guidance.

Acute Renal Failure

Acute kidney injury occurred in 36 patients (23.1%) in the C-144-01 study; 8 (5.1%) experienced Grade 3 and 4 (2.6%) experienced Grade 4 acute kidney injury. There was 1 report of a patient with an event of renal tubular necrosis that was ongoing at the time of death. See 7 Warnings and Precautions for monitoring and management guidance.

Hypersensitivity Reactions

Infusion related reaction occurred in 9 patients (5.8%) in the C-144-01 study; 2 (1.3%) experienced Grade 3 and 1 (0.6%) experienced Grade 4 infusion related rection. There were no reports of fatal infusion related reaction. All cases of infusion related reactions occurred on the day of or the day after AMTAGVI infusion.

Anaphylactic reaction occurred in 2 patients (1.3%) in the C-144-01 study; 1 (0.6%) experienced a Grade 3 and 1 (0.6%) experienced a Grade 4 anaphylactic reaction.

Hypersensitivity occurred in 1 patient (0.6%) and was a Grade 3 event.

Liver function impairment

Hepatobiliary disorders occurred in 61 patients (39.1%) in the C-144-01 study; 17 (10.9%) experienced Grade 3 and 2 (1.3%) experienced Grade 4 hepatobiliary disorders. There was 1 report of a patient with events of ascites and liver injury that were ongoing at the time of death.

Neurological Disorders

Encephalopathy occurred in 32 patients (20.5%) in the C-144-01 study. In 18.0% of patients, encephalopathy occurred within 30 days of the AMTAGVI infusion, while 3.2% of patients developed encephalopathy after 30 days post-AMTAGVI infusion. The median time to onset following the AMTAGVI infusion was 5 days (min, max: 2, 174). Ten patients (6.4%) experienced Grade 3 and 1 (0.6%) experienced Grade 4 encephalopathy. There were no reports of fatal encephalopathy.

Delirium occurred in 22 patients (14.1%) in the C-144-01 study; all events of delirium occurred within 30 days of the AMTAGVI infusion. The median time to onset following the AMTAGVI infusion was 5.5 days (min, max: 2, 18). Six patients (3.8%) experienced Grade 3 delirium. There were no reports of Grade 4 or fatal delirium.

Cytokine release syndrome

Cytokine release syndrome was reported in 5 patients (3.2%) in the C-144-01 study; 2 (1.3%) experienced Grade 3 cytokine release syndrome. There were no reports of Grade 4 or fatal cytokine release syndrome. The time to onset following the AMTAGVI infusion was 1 to 10 days.

Capillary Leak Syndrome and Vascular Hypotensive Disorders

Capillary leak syndrome occurred in 20 patients (12.8%) in the C-144-01 study; 7 (4.5%) experienced Grade 3 capillary leak syndrome. There were no reports of Grade 4 or fatal capillary leak syndrome.

Hypotension occurred in 56 patients (35.9%) in the C-144-01 study; 17 (10.9%) experienced Grade 3 and 2 (1.3%) experienced Grade 4 hypotension. There were no reports of fatal.

Eye Disorders

Eye disorders occurred in 27 patients (17.3%) in the C-144-01 study; 4 (2.6%) experienced Grade 3 eye disorders. There were no reports of Grade 4 or fatal eye disorders. The most commonly reported (≥5%) events included visual impairment (7.1%) and uveitis (5.1%).

Skin and Subcutaneous Tissue Disorders

Skin and subcutaneous tissue disorders occurred in 103 patients (66.0%) in the C-144-01 study; 23 (14.7%) experienced Grade 3 and 1 (0.6%) experienced Grade 4 skin and subcutaneous tissue disorders. There were no reports of fatal skin and subcutaneous tissue disorders. The most commonly reported (≥5%) events included rash (44.2%), alopecia (27.6%), pruritus (15.4%), vitiligo (10.3%), and dry skin (5.8%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

Table 3 summarises the non-laboratory adverse reactions that occurred in at least 10% patients treated with AMTAGVI.

Table 3 – Non-laboratory Adverse Reactions Observed in at Least 10% of Patients with Melanoma Treated with AMTAGVI (N=156)

Adverse Reaction	Any Grade n (%)	Grade 3 or Higher n (%)
Blood and lymphatic system disorders		
Febrile neutropenia	65 (41.7)	65 (41.7)
Cardiac disorders		
Arrhythmia[a]	74 (47.4)	10 (6.4)
Gastrointestinal disorders		
Diarrhoea	50 (32.1)	2 (1.3)
Nausea	40 (25.6)	3 (1.9)
Vomiting[b]	39 (25.0)	1 (0.6)
Constipation	22 (14.1)	0 (0)
Abdominal pain[c]	18 (11.5)	2 (1.3)

Adverse Reaction	Any Grade n (%)	Grade 3 or Higher n (%)
General disorders and administration site conditions		
Chills	117 (75.0)	8 (5.1)
Pyrexia[d]	83 (53.2)	17 (10.9)
Fatigue[e]	75 (48.1)	12 (7.7)
Oedema[f]	71 (45.5)	10 (6.4)
Infections and Infestations	72 (46.2)	36 (23.1)
Infection with pathogen unspecified[g]	45 (28.8)	21 (13.5)
Infections – bacteria[h]	24 (15.4)	11 (7.1)
Infections – viral[i]	16 (10.3)	6 (3.8)
Metabolism and nutrition disorders		
Changes in weight[j]	44 (28.2)	3 (1.9)
Appetite disorder[k]	33 (21.2)	3 (1.9)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[l]	44 (28.2)	5 (3.2)
Nervous system disorders		
Encephalopathy[m]	32 (20.5)	11 (7.1)
Headache[n]	28 (17.9)	1 (0.6)
Dizziness[o]	17 (10.9)	2 (1.3)
Neuropathy peripheral[p]	16 (10.3)	3 (1.9)
Psychiatric disorders		
Delirium[q]	22 (14.1)	6 (3.8)
Insomnia	16 (10.3)	0 (0)
Renal and urinary disorders		
Acute kidney injury[r]	26 (23.1)	12 (7.7)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea[s]	54 (34.6)	11 (7.1)
Hypoxia[t]	36 (23.1)	19 (12.2)
Cough[u]	32 (20.5)	1 (0.6)
Pleural effusion	18 (11.5)	3 (1.9)

Adverse Reaction	Any Grade n (%)	Grade 3 or Higher n (%)
Skin and subcutaneous tissue disorders		
Rash[v]	69 (44.2)	19 (12.2)
Alopecia[w]	43 (27.6)	0 (0)
Pruritus	24 (15.4)	0 (0)
Vitiligo[x]	16 (10.3)	0 (0)
Vascular disorders		
Hypotension[y]	56 (35.9)	19 (12.2)
Haemorrhage[z]	33 (21.2)	9 (5.8)
Hypertension	27 (17.3)	14 (9.0)
Capillary leak syndrome	20 (12.8)	7 (4.5)

Notes: AEs are coded based on MedDRA version 24.0. Grades are based on Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

[a] Arrhythmia includes atrial fibrillation, sinus tachycardia, supraventricular tachycardia, tachycardia, arrhythmia, atrioventricular block second degree, ventricular tachycardia, atrial flutter.

[b] Vomiting includes procedural vomiting, vomiting.

[c] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower.

[d] Pyrexia includes pyrexia, body temperature increased.

[e] Fatigue includes asthenia, fatigue, malaise.

[f] Oedema includes conjunctival oedema, eyelid oedema, macular oedema, periorbital oedema, catheter site oedema, face oedema, generalised oedema, localised oedema, oedema, oedema peripheral, peripheral swelling, brain oedema, vasogenic cerebral oedema, oedema genital, scrotal oedema, pulmonary oedema, lymphoedema.

[g] Infection with pathogen unspecified includes bacteraemia, bronchitis, chronic sinusitis, conjunctivitis, device related infection, diarrhoea infections, encephalitis, endocarditis, enterocolitis infectious, gallbladder abscess, gastrointestinal infection, infection, meningitis, mucosal infection, nasopharyngitis, otitis externa, parametritis, pelvic inflammatory disease, pneumonia, pyuria, rash pustular, respiratory tract infection, rhinitis, sinusitis, skin infection, upper respiratory tract infection, urinary tract infection, vascular device infection.

[h] Infections – bacterial includes bacterial infection, bacteriuria, cellulitis, clostridium bacteraemia, clostridium difficile colitis, clostridium difficile infection, enterobacter bacteraemia, escherichia bacteraemia, escherichia infection, escherichia urinary tract infection, pharyngitis streptococcal, pseudomonas infection, staphylococcal infection.

[i] Infections – viral includes bronchiolitis, COVID-19, cytomegalovirus infection, cytomegalovirus infection reactivation, Epstein-Barr virus infection, gastroenteritis viral, herpes dermatitis, herpes simplex, herpes zoster, herpes zoster meningitis, oral herpes, pneumonia respiratory syncytial viral, respiratory syncytial virus infection, viral infection, viral upper respiratory tract infection.

[j] Changes in weight includes abnormal loss of weight, cachexia, weight decreased, weight increased.

[k] Appetite disorder includes appetite disorder, decreased appetite.

[l] Musculoskeletal pain includes back pain, myalgia, neck pain, pain in extremity, pain in jaw, non-cardiac chest pain, pain, arthralgia, arthritis, bone pain, musculoskeletal chest pain, musculoskeletal discomfort.

[m] Encephalopathy includes depressed level of consciousness, disturbance in attention, encephalopathy, lethargy, memory impairment, somnolence, confusional state, mental status changes, bradyphrenia.
[n] Headache includes headache, tension headache.
[o] Dizziness includes dizziness, dizziness postural, syncope, vertigo.
[p] Neuropathy peripheral includes neuropathy peripheral, paraesthesia, autonomic neuropathy, peripheral motor neuropathy, peripheral sensory neuropathy.
[q] Delirium includes hallucination, hallucination visual, delirium, delusion, disorientation, agitation, restlessness.
[r] Acute kidney injury includes blood creatinine increased, acute kidney injury, oliguria, renal failure.
[s] Dyspnoea includes dyspnoea, dyspnoea exertional, orthopnoea, respiratory distress, wheezing, tachypnoea.
[t] Hypoxia includes oxygen saturation decreased, hypoxia.
[u] Cough includes cough, productive cough.
[v] Rash includes rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash follicular, seborrhoeic dermatitis, dermatitis bullous, rash pruritic.
[w] Alopecia includes alopecia, diffuse alopecia.
[x] Vitiligo includes vitiligo, skin hypopigmentation.
[y] Hypotension includes hypotension, blood pressure systolic decreased, orthostatic hypotension.
[z] Haemorrhage includes blood urine present, cerebral haemorrhage, conjunctival haemorrhage, haematemesis, haematuria, intra-abdominal haemorrhage, mouth haemorrhage, oesophageal haemorrhage, pulmonary alveolar haemorrhage, upper gastrointestinal haemorrhage, ecchymosis, epistaxis, haematochezia, haemobilia, haemorrhage intracranial, melaena, periorbital haemorrhage, rectal haemorrhage, subcutaneous haematoma, tumour haemorrhage, vaginal haemorrhage.

8.3 Less Common Clinical Trial Adverse Reactions

Clinically important adverse reactions that occurred in less than 10% of patients treated with AMTAGVI included the following:
Cardiac disorders: Cardiac failure, acute myocardial infarction, pericardial effusion.
Ear and labyrinth disorders: Deafness, hypoacusis.
Eye disorders: Uveitis. Other eye disorders included Grade 1 or 2 vision blurred, visual impairment, periorbital oedema, visual acuity reduced, retinal haemorrhage, and retinal detachment.
Gastrointestinal disorders: Colitis, ascites.
Hepatobiliary disorders: Drug-induced liver injury, hepatic failure.
Immune system disorders: Anaphylactic reaction, cytokine release syndrome, and hemophagocytic lymphohistiocytosis.
Infections and infestations: Sepsis[a], fungal infection[b].
Injury, poisoning and procedural complications: Infusion related reaction.
Nervous system disorders: Immune effector cell-associated neurotoxicity syndrome, aphasia, facial paralysis, and cerebrovascular accident.
Psychiatric disorders: Depression.
Respiratory, thoracic and mediastinal disorders: Acute respiratory failure, respiratory failure, lung infiltration, and pneumonitis.
Adverse events are reported using MedDRA version 24.0
[a] Sepsis includes Neutropenic sepsis, Sepsis, and Septic shock.
[b] Fungal infection includes Candida infection, Fungal infection, Oral candidiasis, and Vulvovaginal mycotic infection.

8.4 Abnormal Laboratory Findings

Table 4 – Grade 3 or 4 Laboratory Abnormalities Occurring in at Least 10% of Patients with Melanoma Following Treatment with AMTAGVI (N=156)

Laboratory Abnormality	Grades 3 or 4 (%)
Neutropenia	100
Leukopenia	100
Lymphopenia	100
Thrombocytopenia	94.2
Anaemia	71.2
Hypophosphatemia	43.6
Hypoalbuminemia	18.6

Grade 3 or 4 laboratory abnormalities starting from infusion of lifileucel to 30 days post infusion are presented. Grades are based on CTCAE version 4.03.

9 Drug Interactions

9.2 Drug Interactions Overview

No interaction studies have been performed with AMTAGVI.

10 Clinical Pharmacology

10.1 Mechanism of Action

Tumour infiltrating lymphocytes (TIL) are cytotoxic and helper T cells that infiltrate tumours as a component of the immunological response to a patient's cancer. TIL may recognise tumour-specific neoantigens via T-Cell receptor (TCR)-peptide human leukocyte antigen (pHLA) engagement and mediate tumour cell lysis.

The specific mechanism of action of AMTAGVI (lifileucel) is unknown.

10.2 Pharmacodynamics

Pharmacodynamic activity was evaluated by measuring longitudinal changes of cytokines and chemokines (IL-15, IL-6, IL-7, IL-9, IL-10, IL-12(p40), CCL2, CXCL10, IFN-γ, and TNF-α) using plasma samples collected at baseline and post-infusion of AMTAGVI up to Month 3. The mean level of IL-15 and CXCL10 peaked following lymphodepletion and administration of AMTAGVI at Day 1-4, decreased over time, and returned to baseline levels within 1-3 months. Other cytokines and chemokines listed above did not show any noticeable changes. No difference was observed in the cytokines and chemokines level between responding and non-responding patients.

10.3 Pharmacokinetics

The cellular nature of AMTAGVI prevents conduction of conventional pharmacokinetic (PK) studies of absorption, distribution, metabolism, and excretion. Persistence of unique T-cell receptor (TCR) clonotypes from AMTAGVI lots in the peripheral blood were tracked for pharmacokinetic activity.

The proportion of unique TCR clonotypes from the AMTAGVI lots contributing to the peripheral blood TCR repertoire among infused patients was analysed using a semi-quantitative polymerase chain reaction followed by next generation sequencing. The proportion of TCR clones that are composed of clonotypes identified in the product increases from a mean of 16% (n=125) at pre-infusion to 83% at Day 4 after AMTAGVI infusion. The TCR clones declined to 51% at Day 14 (n=51) and remain 37% to 41% from Day 42 (n=120) to month 12 (n=37) post-infusion of AMTAGVI. No significant correlation was found between AMTAGVI persistence and efficacy.

11 Storage, Stability, and Disposal

AMTAGVI is supplied in 1 to 4 infusion bag(s), with each bag containing approximately 100 mL of frozen suspension of tumour-derived T cells in 5% DMSO, 0.5% albumin (human), and 300 IU/mL IL-2 (aldesleukin). Each bag is contained within a protective metal cassette. AMTAGVI is stored in the vapour phase of liquid nitrogen and supplied in a liquid nitrogen cryoshipper.

12 Special Handling Instructions

Product and patient-specific labels are located on both the product infusion bag(s) and the protective shipping cassette(s), which are inside the liquid nitrogen cryoshipper.

- Match the identity of the patient with the patient identifiers on the cassette(s) and infusion bag(s) upon receipt.
- Confirm the number of AMTAGVI cassette(s) and infusion bag(s) matches the total number of cassette(s) and infusion bag(s) on the shipment packing slip.
- Store AMTAGVI frozen in the vapour phase of liquid nitrogen (less than or equal to minus 150°C).
- Thaw AMTAGVI immediately prior to infusion.

Part 2: Scientific Information

13 Pharmaceutical Information

Drug Substance

Non-proprietary name of the drug product(s): lifileucel

Product Characteristics:

AMTAGVI (lifileucel) is an autologous T-cell immunotherapy comprised of a suspension of TIL for intravenous infusion. AMTAGVI is manufactured from resected patient tumour tissue prosected from one or more tumour lesions. Immune cells derived from a patient's tumour(s) are expanded in cell culture, washed, formulated as a cell suspension, and cryopreserved. The product must pass a sterility test before release for shipping as a frozen suspension in 1 to 4 patient-specific infusion bag(s) in individual protective metal cassettes. The product is thawed prior to administration back into the same patient.

AMTAGVI is composed primarily of T cells of the CD4+ T and CD8+ T cell lineages. AMTAGVI may also contain monocytes and other lymphocytes, including B cells and NK cells. AMTAGVI may contain viable melanoma tumour cells from the original tumour tissue used to manufacture the product.

The formulation contains 48% PlasmaLyte A, 50% CryoStor CS10 (resulting in final concentration of 5% dimethyl sulfoxide (DMSO)), 2% of 25% human serum albumin (resulting in a final concentration of 0.5% albumin), and 300 IU/mL IL-2 (aldesleukin).

A single dose of AMTAGVI is provided in 1 to 4 infusion bag(s) containing 100 mL of viable cells per bag in individual protective cassettes.

14 Clinical Trials

14.1 Clinical Trials by Indication

Unresectable or metastatic melanoma that has progressed on or after a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor, and who have no satisfactory alternative treatment options

Table 5 – Summary of Patient Demographics for Clinical Trials in Adult patients with Unresectable or metastatic melanoma that has progressed on or after a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor, and who have no satisfactory alternative treatment options

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Age (range)	Sex
C-144-01	Phase 2, open-label, single-arm, prospective, interventional, multicenter study to assess the efficacy and safety of AMTAGVI for treatment of patients with metastatic melanoma	Single intravenous infusion of AMTAGVI. The median AMTAGVI administered dose was 20.5×10^9 viable cells	Patients that underwent tumour resection: 111 Patients that received AMTAGVI: 89 Patients in Efficacy Set: 87	Overall study:55 (25, 74) Efficacy set: 58 (25, 74)	Overall study: 60 (54.1%) male, 51 45.9%) female Efficacy set: 44 (50.6%) male, 43 (49.4%) female

The efficacy of the AMTAGVI treatment was evaluated in Study C-144-01, a global, multicenter, multicohort, open-label, single-arm clinical trial (NCT02360579).

The study enrolled patients with unresectable or metastatic melanoma (Stage IIIc or Stage IV per the American Joint Committee on Cancer staging manual, 7th edition) who have progressed following at least 1 systemic therapy, including a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor or BRAF inhibitor with MEK inhibitor. Other enrolment criteria included Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, adequate function of organs, including bone marrow, kidneys and liver. The study excluded patients with melanoma of uveal or ocular origin, symptomatic and/or untreated brain metastases, organ allograft or prior cell transfer, chronic systemic steroid therapy, active systemic infections, any form of primary or acquired immunodeficiency, coagulation disorders, Grade 2 or higher hemorrhage within 14 days prior to enrollment (tumour resection), left ventricular ejection fraction less than 45% or New York Heart Association functional classification greater than Class 1, and forced expiratory volume in one second of less than or equal to 60%.

Of the 111 patients in the primary efficacy cohort who underwent tumour resection, 22 patients (19.8%) who underwent tumour harvest did not receive lifileucel. The reasons for not receiving lifileucel included: inability to manufacture AMTAGVI (n=6), disease progression (n=5), death due to disease progression (n=3), start of a new anticancer therapy (n=2), fatal adverse event (AE) related to the lymphodepleting regimen (n=1), AE (n=1), withdrawal of consent and physician's decision (n=2), and meeting the exclusion criteria (n=2).

Among the 89 patients who received AMTAGVI, 2 patients received AMTAGVI that did not meet the protocol pre-specified product specification. There were 87 patients in the efficacy analysis population. The median (min, max) time between tumour harvest and AMTAGVI infusion was 34 days (26, 99). The

median (min, max) duration of the manufacturing process was 23 days (23, 43). Lesion origin of AMTAGVI products included skin, lymph nodes, liver, lung, peritoneal, musculo skeletal, breast, and others.

Of the 87 patients, 87 (100%) received prior anti-PD-(L)1 therapy, 86 (98.9%) had progressive disease for at least a prior anti-PD-(L)1 therapy, 72 (82.8%) received prior anti-CTLA-4 therapy, 68 (78.2%) had progressive disease for at least a prior anti-CTLA-4 therapy, 48 (55.2%) received anti-PD-1/anti-CTLA-4 combination therapy and 24 (27.6%) received a BRAF inhibitor or combination therapy with BRAF and MEK inhibitors. Patients received a median of 3 prior lines of therapy (min, max: 1, 8). The median age was 58 years (min, max: 25, 74 years), with 25.3% age 65 or older, 50.6% were male, 95.4% were white, 2.3% were black, and 1.1% were Asian. Disease characteristics were: Stage IV: 98.9%, BRAF V600 mutation-positive: 27.6%; PD-L1 TPS ≥5%: 23.0%; elevated LDH: 64.4%; brain and/or liver metastases: 50.6%. The median target lesion sum of diameters was 99.5 mm (min, max: 15.7, 552.9). The median number of target and non-target lesions as defined by RECIST 1.1 was 6 (min, max: 1, 16). The performance status prior to tumour procurement was ECOG 0 (71.3%) and ECOG 1 (28.7%).

AMTAGVI was administered following a lymphodepleting regimen consisting of cyclophosphamide 60 mg/kg daily with mesna for 2 days followed by fludarabine 25 mg/m^2 daily for 5 days. Three (3) to 24 hours after AMTAGVI infusion, IL-2 (aldesleukin) was administered at 600,000 IU/kg every 8 to 12 hours for up to 6 doses to support cell expansion in vivo. The median AMTAGVI administered dose was 20.5 × 10^9 viable cells (min, max: 1.3 x 10^9, 72.0 x 10^9). The median number of administered IL-2 (aldesleukin) doses was 6, with 36.8% receiving between 1 and 5 doses of IL-2.

The primary endpoint was objective response rate (ORR) by the Independent Review Committee (IRC) per RECIST v1.1.Secondary endpoints included duration of response (DoR). Efficacy results are summarised in Table 6.

Table 6 – Efficacy Results in Study C-144-01 primary efficacy cohort

Endpoint[a]	**Efficacy Set (N=87)**
Objective Response Rate	
ORR, % (95% CI)[b]	28.7 (19.5, 39.4)
Complete response, n (%)	3 (3.4)
Partial response, n (%)	22 (25.3)

CI, confidence interval; ORR, objective response rate.

[a] Per RECIST v1.1 assessed by Independent Review Committee (IRC).

[b] Number of responders was N=25.

The median time to first response to AMTAGVI was 1.5 months (min, max: 1.3, 4.2). With a median follow-up of 23.5 months, the median DoR was 10.4 months (95% CI: 4.1, not reached; min, max: 1.4+, 26.3+).

The recommended AMTAGVI dosing range was set at 7.5 x 10^9 to 72 x 10^9 viable cells (78 received this dosing range). The median administered AMTAGVI dose was 21.2x10^9 viable cells and the median number of administered IL-2 (aldesleukin) dose was 6 with 39.7% receiving between 1 and 5 doses of IL-2. The ORR was 32.1% (95% CI: 21.9%, 43.6%) with a CR of 3.8% (n=3) and PR of 28.2% (n=22). The median time to initial response to AMTAGVI was 1.5 (min, max: 1.3, 4.2). The median DoR was 10.4 months (95% CI: 4.1, not reached).

Supporting pooled efficacy analysis included 189 patients who underwent tumour resection of whom 33 (17.5%) did not receive lifileucel. The reasons for not receiving lifileucel included: inability to manufacture AMTAGVI (n=8), disease progression (n=9), death due to disease progression (n=4), start of a new anticancer therapy (n=2), fatal AE related to the lymphodepleting regimen (n=2), AE (n=2), withdrawal of consent and physician's decision (n=3), and meeting the exclusion criteria (n=3).

Among the 156 patients who received AMTAGVI, 2 patients who received AMTAGVI that did not meet the protocol pre-specified product specification and 1 patient who received AMTAGVI below the protocol pre-specified dosing range due to anaphylactic reaction were excluded.

The supporting pooled efficacy set included 153 patients. The median administered AMTAGVI dose was 21.1×10^9 viable cells (min, max: 1.2×10^9, 99.5×10^9) and the median number of administered IL-2 (aldesleukin) doses was 6 with 43.1% receiving between 1 and 5 doses of IL-2. The ORR was 31.4% (95% CI: 24.1%, 39.4%) with a CR of 5.2% (n=8) and PR of 26.1% (n=40). The median time to initial response to AMTAGVI was 1.4 months (min, max: 1.3, 4.2). With a median follow-up of 27.6 months, the median DoR was not reached (min, max: 1.4+, 45.0+).

15 Microbiology

AMTAGVI is not an antimicrobial drug.

16 Non-Clinical Toxicology

General toxicology

AMTAGVI is a preparation of autologous, non-genetically modified tumour-infiltrating lymphocytes (TIL). As such, it is patient-specific and does not function across species, precluding its testing in traditional nonclinical pharmacology and toxicology animal models. Early studies of mouse TIL in syngeneic tumour models demonstrated no associated toxicity.

Genotoxicity

No studies have been performed to evaluate the genotoxic potential of AMTAGVI

Carcinogenicity

No carcinogenicity or genotoxicity studies have been conducted with AMTAGVI.

Reproductive and developmental toxicology

No studies have been conducted to evaluate the effects of AMTAGVI on fertility.

17 Supporting Product Monographs

1) [PR]PROCYTOX cyclophosphamide tablets USP: 25 mg, 50 mg; cyclophosphamide for injection: 200 mg, 500 mg, 1000 mg, 2000 mg (powder for injection) per vial, control 155509, product monograph, Baxter Corporation. (2012-09-07)
2) [PR]UROMITEXAN mesna for injection: 400 mg, 1 g ampoules; 1 g, 5 g multi-dose vials, control 164028, product monograph, Baxter Corporation. (2013-08-06)
3) [PR]FLUDARABINE PHOSPHATE FOR INJECTION, USP fludarabine phosphate sterile solution for injection: 25 mg/mL (2 mL per vial), control 253592, product monograph, Accord Healthcare Inc. (2021-09-29)
4) [PR]PROLEUKIN® (aldesleukin lyophilized powder: 22 million International Units per vial), control

261017, product monograph, Iovance Biotherapeutics Manufacturing, LLC. (2025-07-09)

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]AMTAGVI™

lifileucel

This Patient Medication Information is written for the person who will be taking **AMTAGVI**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have questions about the condition this medication is for or want more information about **AMTAGVI**, talk to a healthcare professional.

Serious warnings and precautions box

Severe and fatal adverse reactions have occurred in patients treated with the AMTAGVI treatment:

- Low blood counts that last longer than expected and may cause bleeding; increased risk of infection with symptoms like fever, chills or shivering, cough, shortness of breath, rapid breathing, sore throat, mouth sores, and rapid pulse; tiredness, or weakness.
- Heart problems like heart attack, which can cause chest pain, pressure or discomfort, shortness of breath, and pain in the arm, jaw, or back; or an abnormal, slow, or rapid heartbeat, which can lead to dizziness, shortness of breath, or feeling faint.
- Difficulty breathing or shortness of breath that may require extra medical support.
- The kidneys may suddenly stop working, which may cause decreased urine output, swelling in your legs or other parts of your body, nausea, confusion, or shortness of breath.

AMTAGVI should only be administered in an inpatient hospital setting at a qualified treatment center by a physician experienced in the use of anti-cancer agents.

What AMTAGVI is used for:

For the following indication(s) AMTAGVI has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

- AMTAGVI is used to treat adult patients with a type of skin cancer that cannot be removed surgically or has spread to other parts of the body called unresectable or metastatic melanoma. AMTAGVI is used when your melanoma has not responded or stopped responding to a PD-1 blocking drug either by itself or in a combination, and if your cancer is BRAF mutation positive, a BRAF inhibitor drug with or without a MEK inhibitor drug that also has stopped working, and who have no satisfactory alternative treatment options.

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How AMTAGVI works:

AMTAGVI is a type of medicine called a 'Tumour infiltrating lymphocyte immunotherapy.' The active substance in the medicine is lifileucel, which is comprised of T cells derived from tissue excised from your tumour. Tumour infiltrating lymphocytes are cells produced by the body's immune system that may recognize and kill cancer (tumour) cells.

The ingredients in AMTAGVI are:

Medicinal ingredients: lifileucel

Non-medicinal ingredients:
AMTAGVI is cryopreserved in 5% DMSO, 0.5% albumin (human), and 300 IU/mL IL-2 (aldesleukin).
AMTAGVI may contain trace amounts of gentamicin, streptomycin, and amphotericin B.

AMTAGVI comes in the following dosage form:

AMTAGVI is a cell suspension for intravenous infusion.

A single dose of AMTAGVI contains 7.5 x 10^9 to 72 x 10^9 viable cells suspended in a cryopreservation medium. A single dose is split into 1 to 4 patient-specific infusion bag(s) (100 mL per bag) in individual protective metal cassettes.

Do not use AMTAGVI if:

- you are allergic or hypersensitive to lifileucel or to any ingredient in the formulation, including dimethyl sulfoxide (DMSO).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take AMTAGVI. Talk about any health conditions or problems you may have, including if you:

- Have any lung, heart, liver or kidney problems
- Have low blood pressure
- Have a recent or active infection or other inflammatory conditions including cytomegalovirus (CMV) infection, hepatitis B or C or human immunodeficiency virus (HIV) infection
- Have history of nervous system disease, such as delirium and encephalopathy.
- Are pregnant, think you may be pregnant, or plan to become pregnant
- Are breastfeeding

- Notice the symptoms of your cancer are getting worse
- Have had a vaccination in the past 28 days or plan to have one in the next few months
- Have been taking blood thinner

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Educational material for healthcare professionals and patients related to the risks of capillary leak syndrome, cytokine release syndrome, and neurologic toxicity including immune effector cell-associated neurotoxicity syndrome are available via the Learning Management System.

How you will receive AMTAGVI:

- AMTAGVI is made from your surgically removed tumour.
- Your tumour tissue is sent to a manufacturing center to make AMTAGVI. It takes a little more than a month from the time your tumour tissue is received at the manufacturing center until AMTAGVI is available to be shipped back to your healthcare provider, but the time may vary.
- After your AMTAGVI arrives at your treating institution, your healthcare provider will give you lymphodepleting chemotherapy to prepare your body.
- Approximately 30 to 60 minutes before you are given AMTAGVI, you may be given other medicines. These may include:
  - Medicines for an allergic reaction (anti-histamines)
  - Medicines for fever (such as acetaminophen)
- Your AMTAGVI will be provided in 1 to 4 infusion bag(s) containing 100 mL of viable cells per bag. When your body is ready for AMTAGVI infusion, your healthcare provider will give AMTAGVI to you by intravenous infusion. This usually takes less than one and a half hours.

After getting AMTAGVI:

Beginning 3 to 24 hours after AMTAGVI is given, you may be given up to 6 doses of IL-2 (aldesleukin) every 8 to 12 hours via intravenous infusion. Your doctor may discontinue IL-2 (aldesleukin) infusion any time if you present severe side effects.

You will have to stay in the treatment centre until you have completed the IL-2 (aldesleukin) treatment, and you have recovered from any serious side effects associated with the AMTAGVI treatment.

You should plan to stay within 2 hours of the location where you received your treatment for several weeks after getting AMTAGVI. Your healthcare provider will check to see if your treatment is working and help you with any side effects that occur.

Usual dose:

AMTAGVI is provided as a single dose for infusion containing a suspension of tumour-derived T cells. The dose is supplied in 1 to 4 patient-specific IV infusion bag(s) in individual protective metal cassettes. Each dose contains 7.5×10^9 to 72×10^9 viable cells.

Possible side effects from using AMTAGVI

These are not all the possible side effects you may have when taking AMTAGVI. If you experience any side effects not listed here, tell your healthcare professional.

Very common:

- Nausea, vomiting
- Diarrhoea
- Tired or lack of energy
- Change in appetite
- Muscle pain
- Headache
- A change in the minerals in blood and body fluids
- Hair loss
- Laboratory test results showing increased levels of liver enzymes
- Itching
- High blood pressure
- Low protein in the blood
- Rash
- Patches of skin turning lighter than the surrounding skin (vitiligo)
- Buildup of fluid in the body causing swelling or weight gain

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Infection: Fever, chills or shivering, rapid pulse or depending on the location of infection, you may also experience sore throat, mouth sores, cough, shortness of breath or rapid breathing, or chest pain		✓	✓
Encephalopathy (Disease of the brain that severely alters thinking or a disturbance in mental abilities that results in confused thinking and reduced awareness of the surroundings): Altered thinking, disturbance in mental abilities, confused thinking and reduced awareness of the surroundings		✓	✓

Frequency/Side Effect/Symptom	Talk to your healthcare professional		get immediate medical help
	Only if severe	In all cases	
Anaemia (Decrease in the number of red blood cells): Tiredness or weakness		✓	✓
Thrombocytopenia (Decrease in the number of platelets): Bruising or bleeding		✓	✓
Neutropenia/Febrile neutropenia (Decrease in white blood cell count with or without fever): Increased risk of infection		✓	✓
Capillary leak syndrome: Low blood pressure, which can cause fainting or dizziness or lead to organ failure and death, fever and chills, dizziness or light headedness, fast heartbeat, swelling of the feet, ankles, legs, arms, lung and brain, puffiness around the eyes, feeling very tired or weak		✓	✓
Hypoxia (Low oxygen level in the blood): Shortness of breath, confusion or drowsiness		✓	✓
Heart problems: Chest pain, pressure or discomfort; shortness of breath; pain in the arm, jaw, or back; abnormal, slow, or rapid heartbeat that may cause dizziness, shortness of breath, or feeling faint		✓	✓
Kidney damage: Decreased urine output, shortness of breath, nausea, confusion, or swelling in the legs, ankles, or feet		✓	✓
Hemorrhage, including internal organ hemorrhage: Bleeding from any part of the body, including the inside of the body. Signs of bleeding on the inside of the body may include dizziness, tiredness, difficulty breathing, or pain in one area of the body.		✓	✓

Frequency/Side Effect/Symptom	Talk to your healthcare professional		get immediate medical help
	Only if severe	In all cases	
COMMON			
Respiratory failure/acute respiratory failure: Difficulty breathing or shortness of breath		✓	✓
Infusion related reaction: Fever, chills, fast heartbeat, rash, low blood pressure, difficulty breathing, cough, chest tightness or wheezing		✓	✓
Anaphylactic reaction (Severe allergic reaction)**:** Fever, chills, fast heartbeat, rash, low blood pressure, difficulty breathing, cough, chest tightness or wheezing		✓	✓
Uveitis (Inflammation of the eye)**:** Visual impairment, eye irritation, or inflammation inside the eye that can lead to redness, pain, light sensitivity, blurred vision, and dark floating spots in the field of vision		✓	✓
Cytokine release syndrome: Fever (38°C or higher, which can also be a sign of infection), which may be accompanied by: chills, difficulty breathing, dizziness or light-headedness, fast heartbeat, low blood pressure or fatigue		✓	✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

If you want more information about AMTAGVI:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada Drug Product Database website: (Drug Product Database: Access the database); the manufacturer's website Iovance.com, or by calling 1-833-215-7566.

This leaflet was prepared by Iovance Biotherapeutics, Inc.

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