

MSAC Application 1835

**Lifileucel for the treatment of patients
with previously treated unresectable
or metastatic melanoma**

PICO Set

Population

Describe the population in which the proposed health technology is intended to be used:

AMTAGVI is an 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. AMTAGVI was first TGA approved for this indication on June 4th 2026¹. These patients have limited treatment options available and represent a significant unmet medical need in advanced melanoma management, as they have exhausted standard firstline and often second and later-line therapeutic approaches.

Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed health technology, describing how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the technology:

Patients would initially be diagnosed with metastatic melanoma through comprehensive clinical assessment, advanced imaging studies including CT, PET/-CT, or MRI scans, and histological confirmation of the malignancy². Within the Australian healthcare system, patients are typically managed by medical oncologists at tertiary cancer centres or specialized melanoma treatment centres that have expertise in managing advanced disease.

Patients eligible for lifileucel would have a confirmed diagnosis of unresectable or metastatic melanoma and must have received prior treatment with at least an anti-PD-1 inhibitor. They must demonstrate adequate organ function and performance status suitable for tumour-infiltrating lymphocyte (TIL) therapy, including the ability to tolerate intensive treatment protocols. Critically, patients must have resectable tumour tissue suitable for TIL harvest, as this is the starting material for the manufactured product. Additionally, patients must not have contraindications to interleukin-2 (IL-2), the lymphodepleting preparative regimen of cyclophosphamide and fludarabine, or excipients listed in the Product Information¹.

Within the Australian healthcare pathway, eligible patients would be referred to specialized centres capable of delivering cell therapy. At these centres, patients would undergo tumour resection for TIL harvest, followed by ex-vivo expansion of the tumour infiltrating lymphocytes at our manufacturing facility. Subsequently, patients receive lymphodepleting chemotherapy to prepare their immune system, followed by TIL infusion and IL-2 administration. This entire process requires close coordination between surgical oncology, medical oncology, cell therapy specialists, and intensive care teams.

Provide a rationale for the specifics of the eligible population:

The eligible population has been specifically defined to represent patients with high unmet medical need who have exhausted standard treatment options, including checkpoint inhibitors. This population was carefully selected based on evidence from cohorts 2 and 4 of the pivotal clinical trial (C144-01) that demonstrated both clinical efficacy and an acceptable safety profile for lifileucel in this setting. In the pooled cohorts 2 and 4 of C-144-01 trial, patients had received median of 3.0 prior systemic therapies, with all patients having failed at least one anti-PD1 inhibitor, and patients with BRAF-mutation having being treated with a prior BRAF±MEK inhibitor. The requirement for prior anti-PD-1 and BRAF±MEK therapies align with current PBS treatment paradigms in Australia and ensures that patients have received standard systemic therapy before considering TIL therapy, which represents a more intensive treatment approach. This population definition is consistent with the TGA approved indication 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 inhibitor¹. and aligns closely with clinical

practice patterns in managing advanced melanoma within the Australian healthcare context. By focusing on previously treated patients, the application addresses a clear gap in the therapeutic landscape where treatment options become increasingly limited and clinical outcomes are generally poor.

Intervention

Name of the proposed health technology:

Lifileucel (AMTAGVI®) autologous T cell immunotherapy containing tumour-infiltrating lymphocytes (TIL)

Describe the key components and clinical steps involved in delivering the proposed health technology:

Lifileucel is a one-time autologous cell therapy that involves a multi-step process beginning with tumour tissue procurement, requiring surgical resection or excision of tumour tissue which is performed at specialised centres with appropriate surgical capabilities. The harvested tumour tissue is then transported to our centralized manufacturing facility where the tumour infiltrating lymphocytes undergo ex vivo expansion. Currently, this manufacturing occurs inside the United States.

In Australia, it takes approximately 34 days from the time the tumour tissue is received at the manufacturing centre until AMTAGVI is available to be shipped back to the authorised treatment centre (ATC), but the time may vary¹. During manufacturing billions of tumour-specific T cells are generated from the original tumour sample. After receiving the manufactured cell product, patients undergo lymphodepleting chemotherapy, typically consisting of cyclophosphamide and fludarabine, which prepares the immune environment for TIL infusion. Following this preparatory chemotherapy, patients receive a single intravenous infusion of lifileucel.

After the TIL infusion, patients receive a short-course of IL-2 to support T cell expansion and persistence in vivo. This is followed by intensive monitoring. The entire treatment course requires close monitoring for potential adverse events and typically necessitates a hospitalisation period of approximately two to three weeks.

Identify how the proposed technology achieves the intended patient outcomes:

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. Following manufacturing and infusion billions of polyclonal, patient specific TIL migrate to tumour sites, in which they recognise and target a multitude of individualised, tumour specific neoantigens. Tumour neoantigens are mutated antigens, presented by human leukocyte antigen (HLA) on the surface of the tumour. TIL recognise the tumour-specific neoantigens via T-cell receptor (TCR)-peptide human leukocyte antigen (pHLA) engagement. The TCR:pHLA interaction induces T cell-mediated tumour killing via secretion of cytokines and cytolytic enzymes and cell-mediated killing¹.

³⁻¹² Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?

Yes

Explain whether it is essential to have this trademark component or whether there would be other components that would be suitable:

AMTAGVI® is the registered trademark for lifileucel. Lifileucel is an autologous cell therapy product manufactured using a proprietary process that has been developed and validated by Iovance

Biotherapeutics. There are no other TIL therapies approved by the Therapeutic Goods Administration in Australia.

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient (For example: accessibility, dosage, quantity, duration or frequency):

Yes

Provide details and explain:

There are several important limitations on the provision of lifileucel that must be considered.

Lifileucel is administered as a one-time treatment, which differs substantially from conventional ongoing systemic therapies.

Treatment can only be delivered at specialised centres that possess the appropriate infrastructure for cell therapy, including capabilities for tumour resection, cell therapy administration, and intensive care monitoring. Not all hospitals in Australia will have the necessary facilities or expertise to safely deliver this therapy. Additionally, the current manufacturing process occurs outside Australia, which for Iovance provides careful international coordination and logistics management. Manufacturing capacity is finite, and there may be limitations on the number of treatment slots available at any given time.

A particularly significant consideration concerns the requirement for administration of short-course IL-2 (Proleukin) as part of the regimen: IL-2 is currently not ARTG registered. Iovance intends to submit an marketing authorisation application with the TGA in 2027.

Patient selection criteria also create inherent limitations, as not all patients with advanced melanoma are suitable candidates for TIL therapy. Patients must have accessible tumour tissue available for harvest, adequate performance status to tolerate an intensive treatment regimen, and the overall physical fitness to undergo both lymphodepleting chemotherapy and IL-2 administration. Finally, the treatment requires hospitalisation for the lymphodepletion, TIL infusion, IL-2 administration, and careful monitoring of potential adverse events. This hospitalisation requirement represents both a resource consideration and a practical limitation for patients who may live far from specialized treatment centres.

If applicable, advise which health professionals will be needed to provide the proposed health technology:

Delivery of lifileucel requires a comprehensive multidisciplinary team with diverse expertise. Medical oncologists serve as the primary treatment coordinators and must have extensive experience in managing advanced melanoma and immunotherapy-related complications. Surgical oncologists are essential for performing tumour resection and harvesting tissue for TIL expansion, requiring skill in accessing tumours that may be located in challenging anatomical sites. Cell therapy specialists, who are physicians with specific expertise in cellular therapy administration and management, play a critical role in overseeing the actual TIL infusion and immediate post-infusion period. Intensive care physicians are necessary for managing IL-2 related toxicities and providing the supportive care that may be required during the treatment course. Specialised nursing staff trained specifically in cell therapy protocols and IL-2 administration provide the day-to-day patient care and monitoring. Pharmacists coordinate the preparation of lymphodepleting chemotherapy and IL-2, and manage the complex supportive medication requirements. Pathologists contribute to tumour tissue assessment and quality control processes. This integrated team approach is essential for safe and effective delivery of this complex cellular immunotherapy.

If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:

Given the complexity and potential for adverse events associated with TIL therapy and IL-2 administration, delegation of key responsibilities is limited. While specialised trained nursing staff can perform the actual infusion under direct physician supervision, the overall management, treatment decisions, patient monitoring protocols, and toxicity management cannot be delegated and require physician oversight by specialists experienced in cellular therapy and immunotherapy. The treatment protocol requires real-time clinical judgment and decision making that demands physician-level expertise throughout the treatment course.

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:

Referrals for lifileucel would typically originate from medical oncologists who are actively managing patients with advanced melanoma, who have comprehensive familiarity with the patient's complete treatment history, disease status, performance status, and overall suitability for intensive cellular immunotherapy. Appropriate patient selection requires the depth of knowledge and expertise that comes from medical oncologists who manage advanced melanoma patients on an ongoing basis.

Is there specific training or qualifications required to provide or deliver the proposed service, and/or any accreditation requirements to support delivery of the health technology?

Yes

Provide details and explain:

Specialised training is mandatory for all healthcare professionals involved in lifileucel administration. Treatment centres must undergo site certification by Iovance Biotherapeutics, which includes comprehensive assessment of facilities, personnel, and capabilities. Hospital staff require specific training in the proper handling, storage, and administration of cellular therapy products, which have requirements that differ from conventional pharmaceuticals. Healthcare professionals must develop expertise or receive dedicated training in IL-2 administration and the management of its associated toxicities. Additionally, centres must have access to appropriate intensive care facilities and personnel with expertise in managing the complex medical issues that can arise during lymphodepletion, lifileucel infusion and IL-2 administration. The infrastructure requirements extend beyond personnel to include appropriate facilities for cell therapy storage at specific temperatures, dedicated areas for administration, and comprehensive patient monitoring capabilities.

Indicate the proposed setting(s) in which the proposed health technology will be delivered:

The treatment involves lymphodepleting chemotherapy, cell therapy infusion, and IL-2 administration, all of which necessitate close monitoring and access to intensive supportive care management. Treatment would occur specifically at specialised tertiary cancer centres that have been qualified by Iovance, that have developed the appropriate comprehensive infrastructure, trained multidisciplinary teams, and established protocols for managing this complex therapeutic modality.

Australian treatment centres to be designated as Authorized Treatment Centres (ATCs) by Iovance are required to complete a formal authorisation and qualification process consistent with applicable regulatory expectations and quality system requirements. As part of onboarding, each prospective ATC will engage with Iovance authorisation personnel to conduct a structured Evaluation and Gap Analysis (EGA).

The EGA is a documented assessment intended to verify that the centre has appropriately established, implemented, and controlled infrastructure, qualified personnel, governance oversight, policies,

procedures, workflows, and equipment necessary to safely and consistently support tumour procurement and related activities. The assessment evaluates readiness to ensure patient safety, data integrity, and product quality across all critical steps of the treatment process, including adherence to Chain of Identity and Chain of Custody (COI/COC) requirements.

Is the proposed health technology intended to be entirely rendered inside Australia?

No

Provide additional details on the proposed health technology to be rendered outside of Australia:

Currently, the manufacturing of lifileucel occurs at our centralised facilities located outside of Australia. Following tumour resection performed at an ATC, the tumour tissue is carefully packaged and shipped to the manufacturing facility where the tumour-infiltrating lymphocytes undergo their ex vivo expansion process. Once manufacturing is complete, the finished cryopreserved product is shipped back to Australia under carefully controlled conditions for patient administration. It takes approximately 34 days from the time the tumour tissue is received at the manufacturing centre until AMTAGVI is available to be shipped back to the authorised treatment centre¹. Importantly, all clinical activities including the initial tumour resection, and the treatment regimen (lymphodepleting chemotherapy, TIL infusion, IL-2 administration), and all follow-up care occur entirely within Australia at the designated ATC.

Comparator

Nominate the appropriate comparator(s) for the proposed medical service:

Comparator 1: Ipilimumab plus Nivolumab (IPI-NIVO)

Provide a name for your comparator:

Ipilimumab plus Nivolumab (PD-1 / CTLA-4 combination therapy)

Provide an identifying number for your comparator (if applicable):

PBS listing for nivolumab and ipilimumab combination therapy¹³

Provide a rationale for why this is a comparator:

While nivolumab and ipilimumab have each been available as individual treatment options for advanced melanoma in Australia for several years, the combination of IPI-NIVO has only recently become available in the retreatment setting, following the PBAC's positive recommendation at its September 2025 intracycle meeting for a multi-indication (tumour-agnostic) listing of nivolumab and ipilimumab in immunotherapy-sensitive advanced or metastatic cancers, which removed the previous once-per-lifetime restriction and enabled re-treatment, and which took effect on the PBS from 1 March 2026 under streamlined restriction codes 18070 (nivolumab) and 18071 (ipilimumab).. As a result, widespread use of the combination in this part of the treatment pathway has not yet been fully realised.

Based on key opinion leader (KOL) feedback, it is expected that, nivolumab plus ipilimumab (IPI-NIVO) retreatment will become the most commonly used active treatment option for patients requiring further systemic therapy after prior treatment with IPI-NIVO. Accordingly, the combination represents the most clinically relevant comparator in this setting and is expected to be the principal treatment that lifileucel would replace in eligible patients.

For clarification, the specific comparator is the second- or later line retreatment with IPI-NIVO, where the patient has previously received a prior PD-1 containing therapy (e.g. IPI-NIVO or NIVO-RELA or single agent PD-1). The comparator is not the first-line use of nivolumab and ipilimumab where the patient is PD-1 inhibitor naïve.

Pattern of substitution

Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator?

Partially replace the proposed comparator.

Outline and explain the extent to which the current comparator is expected to be substituted:

For patients for whom IPI-NIVO and lifileucel are both eligible options, either lifileucel or IPI-NIVO could be prescribed based on physician discretion considering patient and disease characteristics, timing of treatment, prior treatment and response, contraindications and other factors. Patients who are eligible for IPI-NIVO may also not be eligible for lifileucel based on specific patient fitness, willingness, and other considerations.

Therefore, we expect that lifileucel could partially replace IPI-NIVO.

Lifileucel is not used in conjunction with the comparator.

Potential Comparator 2: Best Supportive Care (BSC)

Best supportive care was raised as a potential comparator during the Australian KOL Advisory Board (Sydney, 12 June 2026). The advisory board clinicians considered that, in their own clinical practice, they would not likely initiate lifileucel until a patient had fully exhausted IPI-NIVO, including retreatment. In their view, once the combination is exhausted, ipilimumab monotherapy is no longer applicable, and the only remaining active option is cytotoxic chemotherapy, not generally regarded with limited effectiveness and use for this population. On this basis, the advisory board considered that patients reaching lifileucel would, in practice, otherwise receive best supportive care, and that BSC may therefore represent a clinically relevant comparator at the point of use.

On balance, it should also be considered that the approved indication will allow use of lifileucel prior to exhaustion of IPI-NIVO. Additionally, there is limited evidence characterising outcomes with best supportive care in advanced melanoma; the advisory board did not identify any melanoma study reflecting best supportive care in this patient population, which may limit the feasibility of a robust comparison against BSC.

IPI-NIVO is presented as the primary comparator (Comparator 1), with best supportive care identified as a potential comparator reflecting the clinical practice described by the advisory board.

Note on ipilimumab monotherapy not being nominated as a comparator

Ipilimumab monotherapy is not nominated as a separate comparator. Based on feedback from the Australian KOL Advisory Board (Sydney, 12 June 2026), patients who would previously have received ipilimumab monotherapy in this setting are now prescribed IPI-NIVO combination therapy, following the recent PBS retreatment listing of nivolumab and ipilimumab for immunotherapy-sensitive advanced or metastatic cancer (PBAC recommendation, September 2025 intracycle meeting; PBS-listed from 1 March 2026)..

Outcomes

List the key health outcomes (major and minor -prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

Health Benefits:

The health benefit outcomes include objective response rate (ORR), overall survival (OS), progression-free survival (PFS), and duration of response (DOR).

Please note that lifileucel has been approved in its indication based on tumour objective response rate (ORR) and duration of response (DOR); a survival benefit has not yet been demonstrated¹.

Health Harms:

Data will be provided on adverse events, including treatment-emergent adverse events related to different components of the treatment regimen (lymphodepleting regimen, IL-2, and lifileucel), and serious adverse events, across proportion of all, grade 3-4 and grade 5 adverse events for lifileucel. Additionally, emergence of adverse events across time will be provided for lifileucel. Comparable data for comparators will be presented where available.

Resources:

Healthcare resource utilisation outcomes relevant to assessing the proposed medical service, compared with the nominated comparator, include hospitalisation requirements such as length of stay and the need for intensive care support, which have direct implications for health system capacity and costs. Surgery and supportive care requirements during and after treatment, including the use of growth factors, antimicrobials,

blood products, and other adjunctive interventions, are also important resource considerations. Differences in the one-time treatment regimen of lifileucel compared to ongoing treatment, and in monitoring and follow-up requirements represent ongoing resource use beyond the initial treatment period. In addition, the need for subsequent systemic therapies in patients who do not respond or who experience disease progression contributes to downstream healthcare utilisation and costs and should be captured as part of the overall resource impact assessment.

Outcome description -please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

The primary outcomes of interest focus on clinical efficacy as demonstrated through objective tumour response and survival outcomes. The pooled cohorts 2 and 4 of the pivotal trial (c144-01) has demonstrated clinically meaningful objective response rates in a heavily pre-treated patient population that had exhausted standard therapeutic options, face limited treatment alternatives, and whom may have primary resistance to PD-1 inhibitors. Patient management undergoes a significant change as a result of lifileucel treatment, transitioning from a paradigm of ongoing systemic therapy to a onetime cellular therapy approach followed by a monitoring and surveillance phase. For patients who achieve responses, prognosis improves substantially compared to historical outcomes in this heavily pretreated population, with some patients achieving long-term disease control. Quality of life outcomes reflect the complex balance between the burden of intensive treatment delivery during the treatment period and the potential benefits of achieving disease control without the need for ongoing systemic therapy. For responding patients, the elimination of continuous treatment administration may provide quality of life benefits despite the intensive nature of the initial treatment course.

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)?

Superior

Provide a brief rationale for the claim regarding health outcomes:

Lifileucel is claimed to demonstrate improved health outcomes compared to relevant comparators based on the clinical efficacy in heavily pretreated melanoma patients who had limited to no therapeutic alternatives. The pivotal trial has shown meaningful objective response rates in a population where historical outcomes were generally dismal. The potential for durable responses following a one-time treatment, as opposed to requiring ongoing therapy, represents a clinically meaningful difference in the treatment paradigm. The mechanism of action, which harnesses the patient's own tumour-specific immune cells, provides a novel therapeutic approach that may benefit patients who have progressed on checkpoint inhibitors. However, it must be acknowledged that the magnitude of clinical superiority and comprehensive comparative effectiveness will be formally evaluated through indirect treatment comparison methodologies, given the absence of head-to-head randomized trials directly comparing lifileucel to the proposed comparators.

For some people, compared with the comparator(s), does the test information result in:

A change in clinical management? Yes

A change in health outcome? Yes

Other benefits? Yes

Provide a rationale, and information on other benefits if relevant:

Lifileucel represents an advancement in the management of advanced melanoma, providing physicians the option to consider for eligible patients a one-time treatment of T cell therapy which has shown long term durable responses. For patients who respond durably to treatment, the one-time treatment removes the need for continuous drug administration, which may substantially improve quality of life and reduce the ongoing burden of cancer treatment. Additionally, lifileucel provides a novel mechanism of action for patients who have exhausted checkpoint inhibitor and BRAF±MEK inhibitor options, addressing an important unmet need in this population where subsequent treatment options are limited and outcomes are typically poor. Health outcomes improve through achievement of tumour control and the potential for long-term remission in responding patients.

In terms of the immediate costs of the proposed technology (and immediate cost consequences, such as procedural costs, testing costs etc.), is the proposed technology claimed to be more costly, the same cost or less costly than the comparator?

More costly

Provide a brief rationale for the claim:

Lifileucel is expected to have higher costs compared to checkpoint inhibitor therapy due to the higher costs of manufacturing personalised cellular therapy manufacturing, the specialised hospital requirements for managing the tumour tissue and lifileucel product, and the intensive hospital care associated with surgery and cell therapy administration. The manufacturing process requires sophisticated manufacturing facilities and expertise to obtain billions of patient specific T cells from tumour tissue, representing significant investment expended. The treatment delivery requires specialised centres with cellular therapy capabilities, experienced multidisciplinary teams, and intensive care resources. The hospitalisation and intensive monitoring after treatment add to immediate costs. However, it is important to consider that lifileucel is a onetime treatment, and for patients who achieve durable responses, there are no ongoing drug costs or repeated administration costs that accumulate over time. The economic model will provide a comprehensive evaluation of both short term and long-term cost implications, including careful consideration of hospitalisation costs, supportive care requirements, and management of adverse events. The analysis will also incorporate quality-adjusted life years gained, providing a complete picture of the cost-effectiveness profile.

Algorithms

PREPARATION FOR USING THE HEALTH TECHNOLOGY

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:

The clinical pathway begins with initial diagnosis and comprehensive staging of melanoma using advanced imaging studies including CT scans, PETCT, and MRI as clinically appropriate. Patients typically receive first-line systemic therapy, most commonly consisting of anti-PD1 containing therapy such as IPI-NIVO combination therapy, RELA-NIVO, pembrolizumab or nivolumab². For patients whose melanoma harbors BRAF V600 mutations, consideration is given to BRAF and MEK inhibitor combination therapy generally following checkpoint inhibitor therapy, although less commonly a BRAF±MEK inhibitor may also be considered for first-line treatment for bulky or aggressive disease². Following disease progression, comprehensive assessment determines the remaining treatment options available to the patient.

Patients eligible for lifileucel can be referred to specialist melanoma treatment centres that have expertise in managing complex advanced disease and have been authorised by Iovance. A thorough evaluation for TIL therapy eligibility is undertaken, which includes comprehensive performance status evaluation to

ensure the patient can tolerate an intensive treatment regimen, including lymphodepleting chemotherapy and IL-2 administration. Laboratory testing confirms that the patient has adequate organ function. The patient is assessed to ensure availability of resectable tumour tissue suitable for TIL harvest, as viable tumour tissue is essential for the manufacturing process.

Once initial eligibility is established, the case undergoes multidisciplinary team discussion involving medical oncologists, surgical oncologists, cell therapy specialists, and intensive care physicians to develop a comprehensive treatment plan. Throughout this process, detailed patient counselling occurs to ensure the patient understands the complexity of the treatment, potential benefits, risks, and the commitment required. Formal informed consent is obtained before proceeding with treatment.

Is there any expectation that the clinical management algorithm before the health technology is used will change due to the introduction of the proposed health technology?

No

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:

The introduction of lifileucel is not expected to change the clinical management algorithm prior to treatment initiation in the proposed population. Patients eligible for lifileucel will have already been diagnosed with unresectable stage III or stage IV melanoma and will have progressed following standard systemic therapy, including immune checkpoint inhibitor and BRAF±MEK inhibitor based treatment. These patients would already be under specialist oncology care and undergoing routine disease assessment, imaging, and treatment decision-making consistent with current practice.

Lifileucel is positioned as an alternative subsequent-line treatment option within the existing post-progression pathway and does not alter the approach to diagnosis, initial treatment selection, or earlier-line management. While delivery of lifileucel requires additional procedural and logistical steps (such as tumour tissue harvest and coordination with specialised centres), these occur after the decision to treat has been made and do not represent a change to the clinical management algorithm prior to use when compared with the nominated comparator.

USE OF THE HEALTH TECHNOLOGY

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:

Delivery of lifileucel requires substantial healthcare resources that span multiple clinical domains. The process begins with initial assessment by the hospital including physical examination, and workup including complete blood counts, cardiac scans, and CT or MRI scans for tumour assessment. Tumour resection surgery requires operating room time, a skilled surgical team including surgeons and surgical nurses, anaesthesia services, and post-operative recovery facilities.

As part of the treatment regimen, patients undergo lymphodepleting chemotherapy consisting of cyclophosphamide and fludarabine, which requires laboratory tests (creatinine clearance, complete blood counts with differential, serum chemistries, and urinalysis), pharmacy preparation, infusion and associated supportive care including continual monitoring of cardiac, pulmonary and organ function.

Lifileucel is administered in a tertiary hospital setting under the supervision of a physician experienced in the use of anticancer agents. An intensive care facility and specialists skilled in cardiopulmonary or intensive care medicine must be available.

A critical component of the treatment regimen is IL-2, also known as aldesleukin or Proleukin. Cell therapy administration itself requires specialised supplies and equipment for handling and infusing the cellular

product, along with appropriate facilities for maintaining the product at required temperatures until administration.

The treatment course necessitates patient hospitalisation typically lasting two to three weeks, during which patients require intensive monitoring and supportive care. Throughout the treatment period and subsequently, imaging studies are required for response assessment, typically including CT scans or PET-CT at defined intervals. Extensive laboratory monitoring tracks organ function, blood counts, and metabolic parameters.

Supportive care medications represent a significant resource category, including growth factors such as filgrastim for white blood cell recovery, broad -spectrum antimicrobials for infection prevention and treatment, antiemetics for nausea management, and various other medications to support organ function and patient comfort. Blood product support including red blood cells, platelets, and other components may be needed. Following the acute treatment phase, ongoing follow -up care and monitoring continue, along with resources for management of any adverse events that may occur during or after treatment.

Explain what other healthcare resources are used in conjunction with the comparator health technology:

For the comparator IPI-NIVO, healthcare resource utilisation follows a different pattern centred around ongoing outpatient administration. For IPI-NIVO, patients require regular outpatient infusion clinic visits of every three weeks during the induction phase followed by maintenance every 2 or 4 weeks until disease progression, unacceptable toxicity, or treatment cessation for any other reason. Each visit requires premedication to reduce infusion reactions, infusion centre staff time, and supplies for intravenous drug administration¹⁴.

Disease monitoring through imaging studies occurs at regular intervals with IPI/NIVO as per standard care to assess response to therapy and detect progression. Laboratory monitoring before each treatment cycle tracks for potential immune-related adverse events and general organ function. A significant component of care involves management of immune-related adverse events. This management may require corticosteroids and additional immunosuppressive agents, along with specialist consultations when specific organs are affected.

Supportive care medications are needed to manage treatment-related symptoms and complications. For nivolumab and ipilimumab, the treatment continues over an extended period until disease progression, development of unacceptable toxicity, or treatment cessation for any other reason, which may span many months or potentially years in responding patients^{15,16}. Follow-up care maintains continuity of patient monitoring throughout the treatment course. While most care occurs in the outpatient setting, potential hospitalisation may be required for management of severe immune-related adverse events, such as severe colitis, pneumonitis, hepatitis, or endocrinopathies that require intensive management.

Describe and explain any differences in the healthcare resources used in conjunction with the proposed health technology vs. the comparator health technology:

The healthcare resource profiles for lifileucel and checkpoint inhibitor comparators differ substantially in their patterns and intensity. The treatment duration compared to IPI-NIVO represents perhaps the most fundamental difference. Lifileucel is a onetime treatment with intensive upfront resource utilisation concentrated in a relatively short period, whereas IPI-NIVO combination therapy requires ongoing administration over many months to years, with resource utilisation distributed across this extended timeframe but accumulating continuously^{17,18}.

The setting of care differs, with lifileucel requiring hospitalisation in facilities with intensive care capabilities and specialised cell therapy infrastructure, while the comparators are administered in standard out-patient infusion centres. Lifileucel has specific surgical requirements for tumour resection that are not part of standard checkpoint inhibitor therapy. The specialized infrastructure needs for lifileucel extend to

cell therapy storage capabilities, handling procedures, and expertise in IL-2 administration, whereas the comparator uses conventional infusion clinic infrastructure without need for specialized cellular therapy capabilities.

The intensity of monitoring differs substantially between approaches. Lifileucel requires monitoring during the treatment period with continuous assessment of hemodynamic status, organ function, and potential complications, whereas the comparator involves routine outpatient monitoring with periodic clinic visits and laboratory testing. The requirement for IL-2 as part of the lifileucel regimen adds complexity and resource requirements not present with the comparator, including the need for intensive care capabilities and specialized expertise in managing IL-2 related toxicities. For patients who respond to lifileucel, subsequent resource utilisation is limited primarily to surveillance, whereas IPI-NIVO combination therapy requires ongoing drug administration resources and management of AEs for as long as the patient continues to benefit from treatment^{17,18}.

CLINICAL MANAGEMENT AFTER THE USE OF HEALTH TECHNOLOGY

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, after the use of the proposed health technology:

Following lifileucel and IL-2 administration, patients remain in the in-patient setting for an extended monitoring period, which lasted a mean of REDACTED days from data collected in Cohort 4 of study C-144-01¹⁹. During this time, active management focuses on addressing and resolving treatment-related adverse events, which may include cytopenias, infections, hemodynamic changes related to IL-2, and other potential complications. Patients receive intensive supportive care until they are medically stable enough for discharge.

Ongoing clinical follow-up appointments are scheduled for the purpose of monitoring of long-term outcomes, assessment of any late-developing complications, and providing continued support to the patient.

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, after the use of the comparator health technology:

Following initiation of the comparator therapies, patients continue treatment administration according to the approved dosing schedule, which involves regular infusion centre visits. Regular imaging for response assessment occurs at defined intervals as per standard of care to monitor disease status and guide ongoing treatment decisions. Continuous monitoring for immune-related adverse events is maintained throughout the treatment course, as these complications can emerge at any time during therapy and occasionally even after treatment discontinuation¹⁴.

Management of toxicities occurs as they arise, with implementation of treatment guidelines for immune-related adverse events that may include corticosteroids, immunosuppressive agents, and treatment interruption or discontinuation depending on severity^{15,16}. For IPI-NIVO combination therapy, the duration of therapy in responding patients can extend for many months or even years, requiring sustained resource commitment for drug administration and monitoring.

For patients whose disease progresses, consideration is given to alternative treatment options based on available therapies and patient characteristics. Patients who discontinue therapy due to toxicity require ongoing management of immune-related adverse events, which may necessitate prolonged immunosuppressive therapy and monitoring until resolution^{15,16}. Long-term follow-up continues for all patients to assess response durability in those who benefit from treatment and to monitor for late immune-related complications. Subsequent therapy selection occurs as appropriate when patients eventually experience disease progression, though options may be limited in this heavily pre-treated population.

Describe and explain any differences in the healthcare resources used after the proposed health technology vs. the comparator health technology:

The posttreatment resource requirements differ substantially between lifileucel and checkpoint inhibitor therapy, reflecting their fundamentally different treatment paradigms. Lifileucel requires higher upfront health resources including tumour resection surgery and administration of the treatment regimen, and for the monitoring post-infusion, which lasted a mean of REDACTED days from data collected in Cohort 4 of study C-144-01¹⁹. For patients who respond to lifileucel, ongoing treatment related resource utilisation is minimal beyond surveillance imaging and periodic clinic visits for monitoring. There are no continuous drug administration costs, no repeated infusion centre visits for treatment, and no ongoing costs associated with repeated drug dispensing and handling and late onset AEs. This contrasts especially with IPI-NIVO combination therapy, where responding patients continue to consume treatment-related resources for the entire duration of therapy benefit, which may extend for many months or years¹⁴.

The long-term toxicity profiles differ meaningfully between the approaches. Lifileucel toxicities are predominantly acute in nature and generally resolve following the treatment period, with most patients recovering normal organ function and blood counts within weeks of treatment. While follow-up monitoring continues, it is primarily surveillance-focused rather than active toxicity management. In contrast, checkpoint inhibitors can cause delayed immune-related adverse events that may emerge months after treatment initiation or even after treatment discontinuation, requiring ongoing vigilance and potential long-term management with immunosuppressive medications.

Subsequent therapy requirements may differ based on response patterns and durability. For lifileucel non-responders or patients who eventually progress, subsequent therapy must be selected from remaining available options. For checkpoint inhibitor patients who progress, the treatment history and sequence may influence subsequent therapy choices differently. The patterns of response and progression may differ between the treatment modalities, potentially affecting downstream treatment requirements and resource utilisation.

Healthcare resource use for best supportive care, if considered a comparator, is minimal as this focuses on symptom management, palliative care, palliative radiotherapy, along with emotional and practical support.

Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology:

Diagrams have been developed to illustrate the clinical management algorithm for melanoma in Australia, both without and with the availability of lifileucel, and will be included in the final submission².

The current clinical management pathway begins with presentation of a suspicious skin lesion, followed by biopsy or excision biopsy, histopathological confirmation of melanoma, and staging based on Breslow thickness and pathological assessment. Patients with localised disease are managed according to established surgical and adjuvant treatment guidelines, while patients with unresectable stage III or stage IV disease enter the systemic therapy pathway¹.

In current practice, first-line systemic treatment for advanced melanoma typically consists of immune checkpoint inhibitor therapy, including anti-PD-1 monotherapy (pembrolizumab or nivolumab) or combination IPI-NIVO, and RELA-NIVO with treatment selection influenced by patient characteristics and disease factors. For patients with BRAF V600 mutation-positive disease, BRAF-MEK targeted therapy combinations (dabrafenib plus trametinib, vemurafenib plus cobimetinib, or encorafenib plus binimetinib) may be used either before or after immunotherapy. Consultation with KOLs indicate BRAF-MEK targeted therapy occurs after immunotherapy. Patients are assessed for treatment response and disease progression, with ongoing follow-up and monitoring¹.

For patients who experience disease progression following immunotherapy and, where relevant, BRAF+/- MEK targeted therapy, current management options are limited and may include further immunotherapy (if not previously received), cytotoxic chemotherapy (e.g. dacarbazine or temozolomide), combination

chemotherapy regimens, clinical trial participation, or best supportive care¹. IPI-NIVO retreatment is now also a PBS-subsidised treatment option, following its revised listing from 1 March 2026 for these patients¹³.

The proposed treatment pathway incorporating lifileucel integrates tumour-infiltrating lymphocyte (TIL) therapy as a subsequent-line option for patients with unresectable stage III or stage IV melanoma who have progressed after standard systemic therapies. In this pathway, eligible patients are identified following progression on prior immunotherapy (and targeted therapy where applicable), referred to a specialist centre, and assessed for suitability for lifileucel. Lifileucel is positioned alongside other post-progression options, and is intended to provide an effective disease-modifying treatment option for patients with limited remaining alternatives.

Figure 1 Treatment pathway of malignant melanoma patients

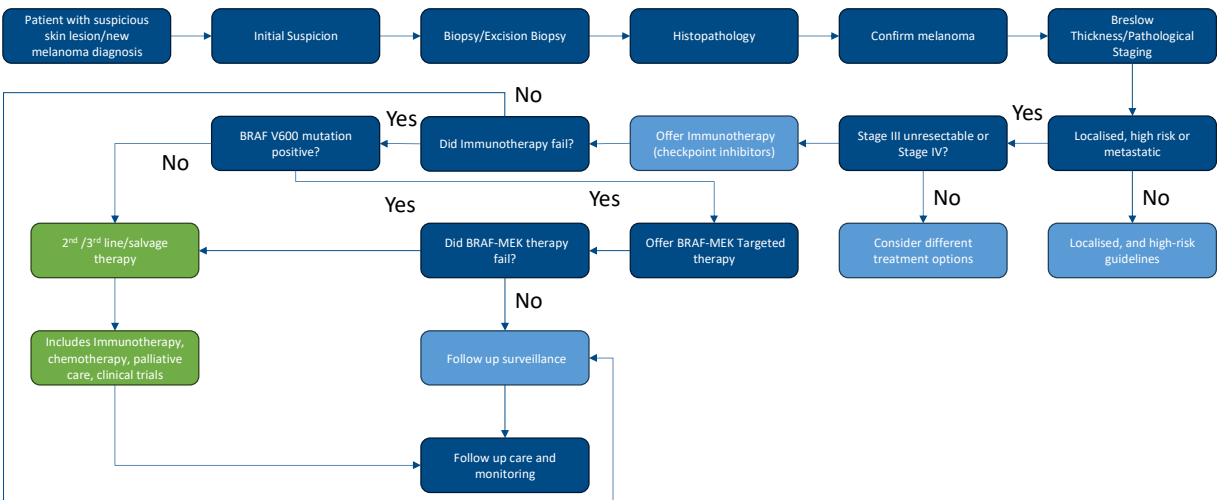
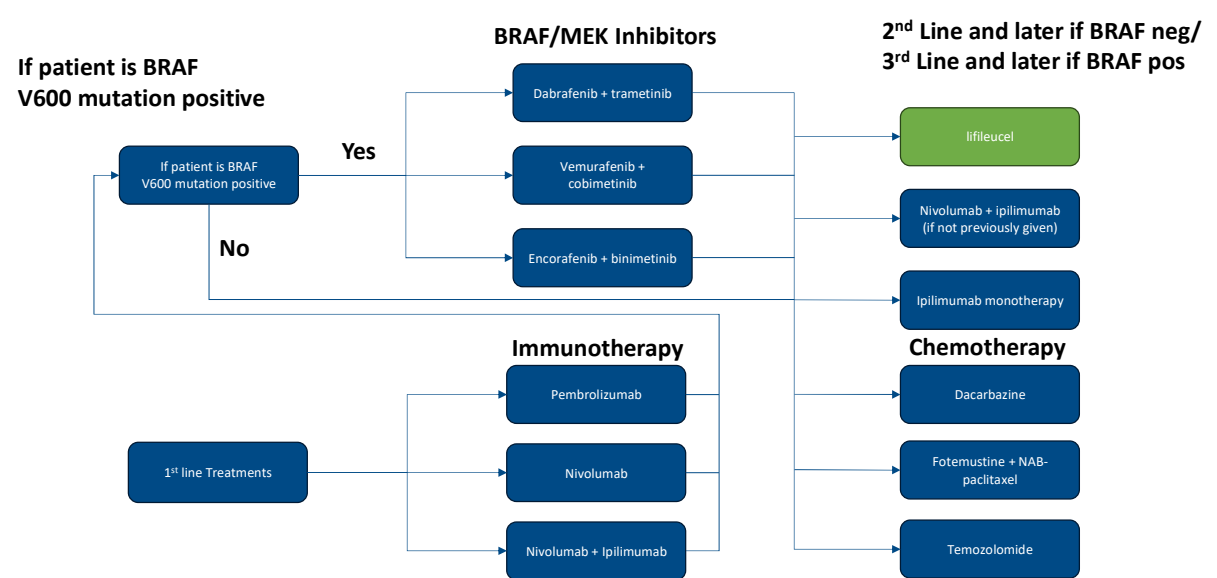


Figure 2 Systematic therapies for malignant melanoma patients



Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology:

The clinical evidence supporting use of the proposed health technology is based primarily on Cohorts 2 and 4 of study C-144-01 (NCT02360579), a prospective, multicentre, open-label, non-randomised Phase 2 study evaluating lifileucel, an autologous tumour-infiltrating lymphocyte (TIL) therapy, in adults with previously treated unresectable or metastatic melanoma (Figure 3). The study population was heavily pretreated, with high prior exposure to immune checkpoint inhibitors, including anti-PD-1 therapy, and additional systemic therapies in many patients.

The pivotal evidence is reported in the 5-year follow-up analysis of pooled cohorts 2 and 4 (n=153) published by Medina et al. (2025)²⁰ in the Journal of Clinical Oncology (Figure 4), and Chesney et al. (2022)²¹ in the Journal for Immuno-Therapy of Cancer which covered a median follow-up of 27.6 months. Patients underwent tumour harvest followed by central manufacture of lifileucel, non-myeloablative lymphodepleting chemotherapy, a single lifileucel infusion, and protocol-specified supportive care including IL-2. The primary endpoint was objective response rate (ORR), with secondary endpoints including duration of response (DoR), progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and safety¹⁸.

Results from the 5-year analysis demonstrated clinically meaningful and durable tumour responses in this heavily pretreated population. Long-term follow-up showed evidence of sustained benefit, with a long-term survival plateau and 19.7% of patients alive at 5 years²⁰. The most common grade 3/4 treatment-emergent adverse events ($\geq 30\%$) were thrombocytopenia (76.9%), anaemia (50.0%), and febrile neutropenia (41.7%)²¹.

Study C-144-01 demonstrates the efficacy and durability of lifileucel in a population with advanced melanoma and limited remaining treatment options. While the evidence base is derived from a single-arm study design, the availability of long-term follow-up data support the clinical relevance of the observed outcomes. Comparative effectiveness will be assessed through an indirect treatment comparison, the methodology and results of which will be presented in the economic evaluation.

Figure 3 Study details of pivotal trial

Domain	Details (JCO-25-00765 / C-144-01 5-year analysis)
Trial / identifier ¹	C-144-01; NCT02360579
Design	Phase 2, prospective, multicentre, open-label, non-randomised; single-arm.
Population	Previously treated unresectable/metastatic melanoma; heavily pretreated; high prior ICI exposure.
Sample	5-year analysis presented for pooled cohorts 2 and 4 (n=153).
Prior therapy burden	Median prior systemic therapies 3.0; 153 (100%) had prior anti-PD-1/PD-L1 therapy, 39 (25.5%) had prior BRAF±MEK, 125 (81.7%) had prior anti-CTLA-4 therapy, and 109 (71.2%) had primary resistance to anti-PD-1/PD-L1 as defined by SITC (Society for Immunotherapy of Cancer) criteria
Intervention pathway	Tumour harvest, central manufacturing, lymphodepletion, lifileucel infusion, IL-2, and post-infusion monitoring.

¹ <https://clinicaltrials.gov/study/NCT02360579?cond=NCT02360579&rank=1>

Domain	Details (JCO-25-00765 / C-144-01 5-year analysis)
Follow-up	Median follow-up ~58 months at data cut.
Primary endpoint	Objective response rate (ORR).
Key secondary endpoints	DoR, PFS, OS; safety.

Figure 4 Identified published literature

Study	Medina et al. 2025 ²⁰	Chesney et al. 2022 ²¹
Study (citation)	Medina T, Chesney JA, Kluger HM, Hamid O, Whitman ED, Cusnir M, Thomas SS, Wermke M, Domingo-Musibay E, Phan GQ, Kirkwood JM, Larkin J, Weber J, Graf Finckenstein F, Chou J, Gastman B, Wu X, Fiaz R, Sarnaik AA; C-144-01 Investigators. 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 Nov 20;43(33):3565-3572.	Chesney J, Lewis KD, Kluger H, Hamid O, Whitman E, Thomas S, Wermke M, Cusnir M, Domingo-Musibay E, Phan GQ, Kirkwood JM, Hassel JC, Orloff M, Larkin J, Weber J, Furness AJS, Khushalani NI, Medina T, Egger ME, Graf Finckenstein F, Jagasia M, Hari P, Suler G, Shi W, Wu X, Sarnaik A. 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 Dec;10(12):e005755.
Study design / setting	Prospective, multicentre, open-label, non-randomised Phase 2 trial (C-144-01; NCT02360579).	Same
Population	Adults with unresectable/metastatic melanoma, previously treated with ICIs (PD-1 containing regimen) ± BRAF+/- MEK targeted therapy; heavily pretreated.	Same
Intervention	Lifileucel (autologous TIL therapy) following non-myeloablative lymphodepletion and supportive regimen (incl. IL-2 per protocol).	Same.
Comparator	None (single-arm).	Same
Key endpoints	ORR, DoR, PFS, OS; safety.	Same
Key results (high level)	Durable responses observed; long-term survival plateau signal with ~20% alive at 5 years; 13.9 months median OS reported; no new/late-onset AEs attributed to lifileucel in long-term follow-up. (ClinicalTrials.gov); long-term survival plateau signal with ~20% alive at 5 years;	Reports a clinically meaningful ORR with durable responses at a 27.6 month follow-up

	median OS reported; no new/late-onset AEs attributed to lifileucel in long-term follow-up. (ClinicalTrials.gov)	
Notes / limitations	Single-arm design, heavily pre-treated population	Same analysis set as Medina (2025), at an earlier data cut with median follow-up of 27.6 months.

Identify yet -to-be published research that may have results available in the near future (that could be relevant to your application):

Iovance has initiated an additional relevant study with lifileucel in melanoma patients: IOV-MEL-301.

IOV-MEL-301 (TILVANCE-301, NCT05727904) is a global, multi-centre, randomized, open-label, Phase 3 study evaluating the efficacy and safety of lifileucel in combination with pembrolizumab compared to pembrolizumab monotherapy in patients with previously untreated, unresectable or metastatic melanoma. Study centres in Switzerland and other European countries, among others, are currently actively recruiting patients. A first interim data cut is planned for Q3 2028.

This PICO Set represents preliminary information for the MSAC application for lifileucel (AMTAGVI) and will be refined based on pre-application consultation with MSAC Secretariat and further clinical and economic evidence development. The information contained herein reflects current understanding of the Australian treatment landscape, clinical evidence, and implementation considerations. Final submission materials will incorporate feedback from stakeholder consultations and the most current available evidence.

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