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Lifileucel (AMTAGVI®) for previously treated unresectable or metastatic melanoma

Health Technology Assessment

Final report

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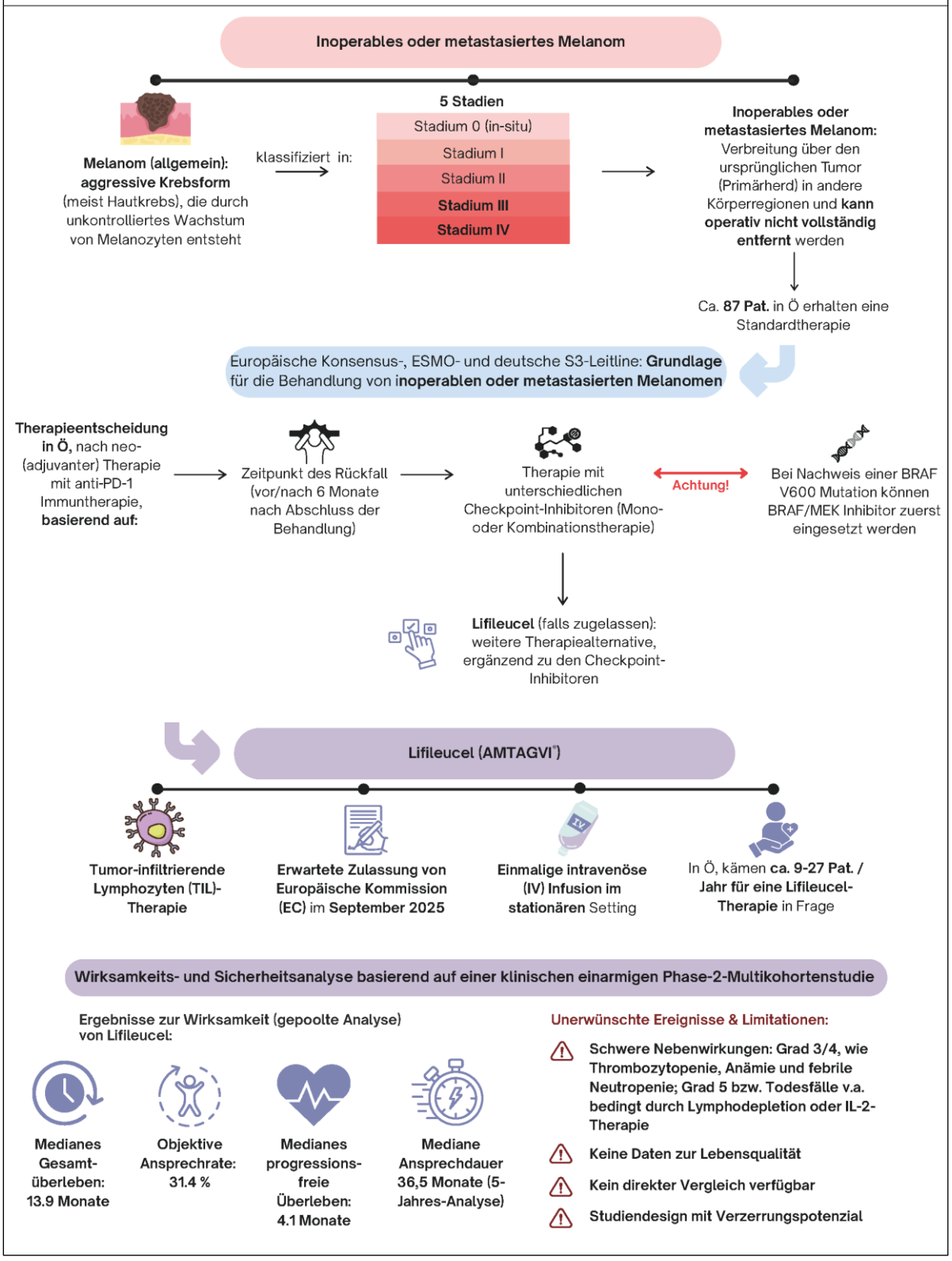
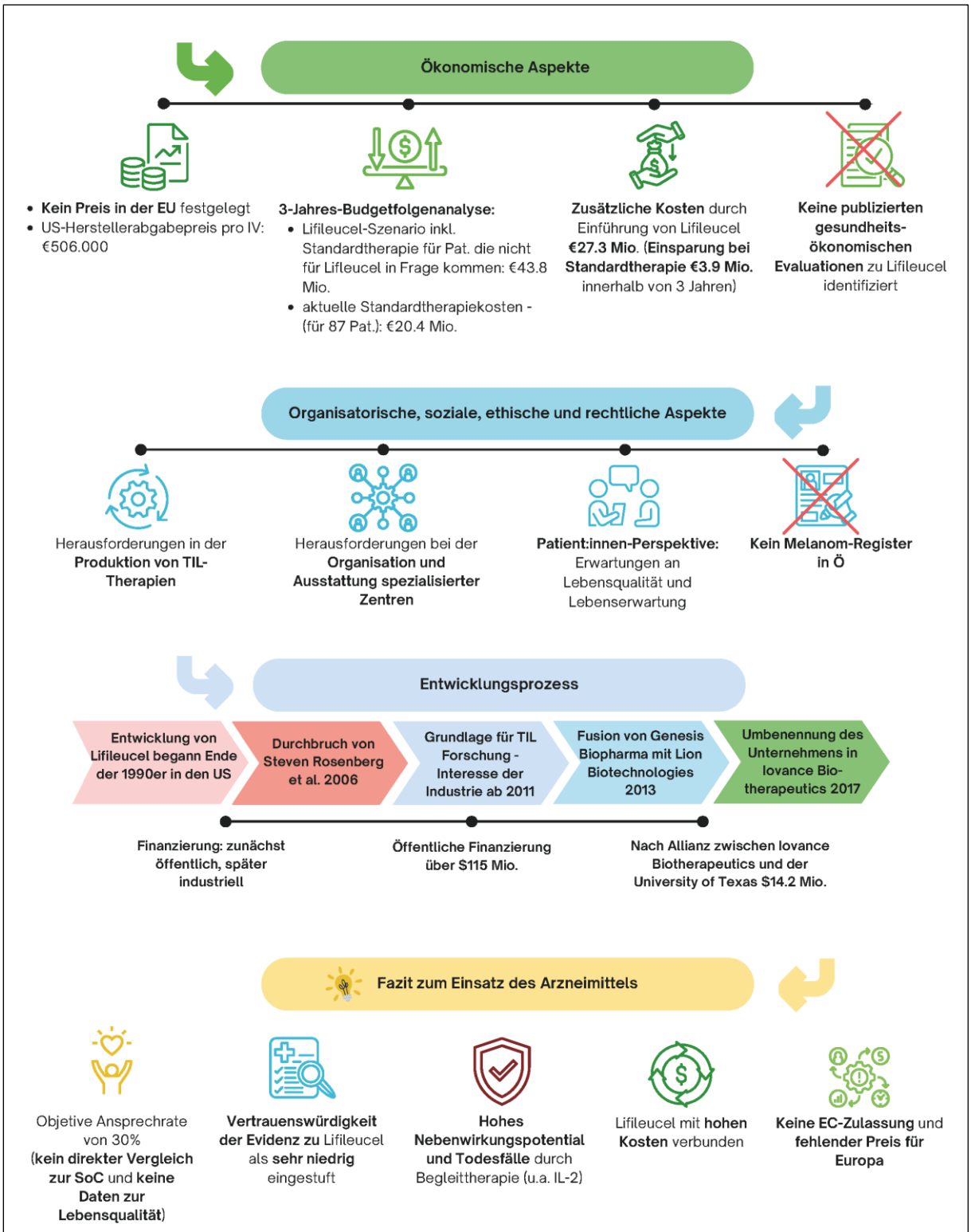
Bewertung des Health Technology Assessments (HTA): Lifileucel für die Behandlung von Patient:innen mit inoperablem oder metastasiertem Melanom, die zuvor mit anti-PD-1-Therapie und bei BRAF-V600-Positivität mit BRAF-Inhibitoren mit oder ohne MEK-Inhibitor behandelt wurden.





ABKÜRZUNGEN

Anti-PD-1...anti-programmierter Zelltod-Protein 1, BRAF...v-Raf murines Sarkom-virales Onkogen-Homolog B1, EC...Europäische Kommission (eng. European Commission), EMA...Europäische Arzneimittel-Agentur (European Medicines Agency), HTA...Health Technology Assessment, IL-2...Interleukin-2, IV...intravenös, MEK...Mitogen-aktivierte Proteinkinase (eng. mitogen-activated protein kinase), Ö...Österreich, Pat....Patient:innen, SoC...Standardtherapie (eng. standard of care), TIL...tumorinfiltrierende Lymphozyten, US...Vereinigte Staaten (eng. United States)

Zusammenfassung

Der vorliegende Health Technology Assessment (HTA) Bericht evaluiert Lifileucel (AMTAGVI®) zur Behandlung von Patient:innen mit vorbehandeltem inoperablem oder metastasiertem Melanom.

Beschreibung der Erkrankung und Behandlungsoptionen

Das Melanom entsteht durch unkontrolliertes Wachstum von Melanozyten, jenen Zellen, die das hautfarbbestimmende Pigment Melanin produzieren. Diese aggressive Krebsart entwickelt sich durch verschiedene Risikofaktoren wie persönliche Krankengeschichte, genetische Veranlagung sowie Umwelt- und UV-Exposition. Die Erkrankung wird nach dem international anerkannten TNM-Staging-System des American Joint Committee on Cancer (AJCC) in fünf Stadien (0-IV) klassifiziert, basierend auf Tumorgröße (T), Lymphknotenbefall (L) und Fernmetastasen (M). Ein fortgeschrittenes Melanom (inoperabel oder metastasiert) hat sich über den Primärherd hinaus ausgebreitet und kann oft durch eine Operation nicht vollständig entfernt werden. Es schließt Krankheitsstadium III (wenn regionale Lymphknoten befallen sind oder In-Transit-Metastasen vorhanden sind) und Krankheitsstadium IV (mit Fernmetastasen in Organen, entfernten Lymphknoten oder der Haut) ein. Die Prognose hängt von verschiedenen histologischen und klinisch-pathologischen Faktoren ab. Im Jahr 2023 lebten in Österreich 27.357 Menschen mit einem Melanom. Etwa 1.845 Neudiagnosen und etwa 399 Todesfällen wurden im Jahr 2022 berichtet. Informationen über die Verteilung der Patient:innen auf die einzelnen Stadien liegen nur für eine begrenzte Anzahl europäischer Länder vor, doch schätzt man, dass im Durchschnitt 9 % bei der Diagnose das Stadium III und 7 % das Stadium IV aufweisen. Für die Behandlung stehen verschieden Leitlinien zur Verfügung u. a. die „European consensus-based interdisciplinary guideline for melanoma“, die „European Society for Medical Oncology“ (ESMO)-Leitlinie und die deutsche S3-Leitlinie (wird derzeit aktualisiert), welche auch Berücksichtigung durch österreichischen Kliniker:innen finden. Weiters verfügbar ist „The American National Comprehensive Cancer Network“ (NCCN)-Leitlinie.

Gemäß den Leitlinien erfolgt in Österreich im Fall eines Hoch-Risiko Primärtumors im Stadium IIB/IIC oder bei operabler Metastasierung eines Melanoms eine adjuvante/neoadjuvante Therapie mit einem Antikörper gegen das programmierte Zelltod-Protein 1 (anti-PD-1) als Monotherapie oder in Kombination mit anderen Checkpoint-Inhibitoren. Bei Vorliegen einer BRAF V600 Mutation kann im Stadium III auch eine adjuvante Therapie mit Dabrafenib/Trametinib zur Anwendung kommen. Im operabel metastasierten Stadium richtet sich die Erstlinientherapie danach, ob zuvor eine adjuvante/neoadjuvante Therapie erfolgt ist, nach dem Zeitpunkt des Rückfalls (<6 oder ≥6 Monate nach Vortherapie) und vorhandenen Mutationen. Verschiedene Checkpoint-Inhibitor-basierte Immuntherapien stehen zur Verfügung und stellen bei nicht vorbehandelten Patient:innen die Therapie der Wahl dar. Bei Vorliegen einer BRAF V600 Mutation wird, falls schon eine PD-1 basierte Therapie im adjuvanten/neoadjuvanten Setting erfolgt ist, auch eine Therapie mit BRAF-Inhibitoren in Kombination mit MEK-Inhibitoren (Mitogen-aktivierte Proteinkinase-Kinase) als zielgerichtete Therapie vor einer Immuntherapie eingesetzt.

Überblick über das neue Arzneimittel

Lifileucel ist eine autologe Therapie mit tumorinfiltrierenden Lymphozyten (TIL), bei der T-Zellen aus dem Gewebe der Patient:innen isoliert, ex-vivo expandiert und reinfundiert werden. Dies ermöglicht eine personalisierte Antitumorreaktion. Die Behandlung erfolgt als einmalige Patient:innen-spezifische intravenöse Infusion mit 7,5 bis 72 x 10^9 lebensfähigen Zellen und erfordert eine stationäre Aufnahme unter Aufsicht erfahrener Ärzt:innen sowie Zugang zu Intensivstation und Notfallmedizin. Die Therapie gliedert sich in drei Phasen: Prä-Infusion (multidisziplinäre Beurteilung, Tumorresektion, vorbereitende Lymphodepletionstherapie), Infusion (Prämedikation mit myeloreduktiver Lymphodepletion, Lifileucel-Verabreichung und Überwachung), sowie Post-Infusion (erneute Beurteilung, Interleukin-2/IL-2-Therapie mit einem nach der Lifileucel-Applikation nochmals 10–14-tägigem Krankenhausaufenthalt, d. h. insgesamt ca. 3 Wochen).

Lifileucel befindet sich derzeit im Zulassungsverfahren der europäischen Arzneimittelbehörde (European Medicines Agency, EMA), mit erwarteter Genehmigung durch die Europäische Kommission im September 2025. Die geplante Indikation umfasst die Behandlung von Erwachsenen mit vorbehandeltem inoperablem oder metastasiertem Melanom. Die FDA (United States Food and Drug Administration) hat Lifileucel bereits im Februar 2024 für Patient:innen mit inoperablem oder metastasiertem Melanom zugelassen, die zuvor mit anti-PD-1-Therapie und bei BRAF-V600-Positivität mit BRAF-Inhibitoren (mit oder ohne MEK-Inhibitor) behandelt wurden.

Österreichische Kliniker:innen schätzen, dass die Zahl der für Lifileucel geeigneten Patient:innen von neun im ersten Jahr auf 27 im dritten Jahr nach Markteinführung ansteigen könnte.

Wirksamkeit und Sicherheit

In einer multizentrischen, offenen, einarmigen Phase-2-Multikohortenstudie wurde die Wirksamkeit von Lifileucel bei Patient:innen mit einem zuvor behandelten, metastasierten oder inoperablen Melanom untersucht. Die gepoolte Analyse zweier Kohorten ergab eine komplette Ansprechrate von 5 %, eine partielle Ansprechrate von 26 %, sowie eine stabile Krankheitsrate von 46 %. Insgesamt betrug die objektive Ansprechrate 31,4 %. Die mediane Gesamtüberlebenszeit betrug 13,9 Monate, die progressionsfreie Überlebenszeit 4,1 Monate. Bei allen Patient:innen trat mindestens ein behandlungsbedingtes unerwünschtes Ereignis auf, darunter am häufigsten Thrombozytopenie (76,9 %), Anämie (50,0 %) und febrile Neutropenie (41,7 %). Sechs Patient:innen starben innerhalb von 30 Tagen nach der Lifileucel-Infusion, von denen vier als behandlungsbedingt durch die Begleittherapie (Lymphodepletion und IL-2) eingestuft und zwei auf Krankheitsprogression zurückgeführt wurden.

Die ESMO-Magnitude of Clinical Benefit Scale (MCBS) wurde für Lifileucel aufgrund von Bedenken hinsichtlich der Toxizität mit einem Score von 2/5 eingestuft, was auf keinen bedeutenden klinischen Nutzen hinweist. Zudem wurden keine Daten zur Lebensqualität erhoben. Aufgrund des offenen Studiendesigns, der fehlenden Vergleichsgruppe und der unangemessenen retrospektiven Zusammenlegung der Kohorten wurde die methodische Qualität der Studie als moderat eingestuft. Insgesamt wurde die Vertrauenswürdigkeit der Evidenz mit GRADE (Grading of Recommendations, Assessment, Development and Evaluation) als niedrig bis sehr niedrig eingestuft.

Ökonomische Aspekte

Für Lifileucel ist in Europa noch kein Preis festgelegt. Das vertriebsberechtigte Unternehmen hat einen amerikanischen Herstellerabgabepreis von $ 563.000 (umgerechnet € 506.000) angegeben. Eine vom Unternehmen durchgeführte ungenaue Budgetimpact-Analyse zu Lifileucel ergab Kosten zwischen € 5 bis € 10 Millionen. Die Berechnung bezieht sich nicht auf österreichische Daten.

Auf Basis der für den österreichischen Kontext durchgeführten Budgetfolgenanalyse (vor Preisverhandlungen) im Rahmen der HTA-Berichterstellung, belaufen sich die direkten medizinischen Kosten inklusive notwendiger Zusatzbehandlungen bei einer geschätzten Patient:innen-Anzahl von 17 auf etwa € 9.1 Millionen jährlich beziehungsweise € 27.3 Millionen über drei Jahre. Werden auch die SoC-Kosten für die Patient:innen, die nicht für Lifileucel in Frage kommen, berücksichtigt, so ergeben sich im Lifileucel-Szenario Gesamtkosten von € 14,6 Millionen pro Jahr und € 43,8 Millionen für die Jahre 1–3. Im Vergleich dazu kostet das aktuelle SoC-Szenario bei einer geschätzten Patient:innen-Anzahl von 87 hingegen rund € 6,8 Millionen pro Jahr und etwa € 20,4 Millionen über drei Jahre.

Öffentliche Investition

Die Entwicklung von Lifileucel zur Behandlung des inoperablen Melanoms begann Ende der 1990er Jahre am National Cancer Institute (NCI) in den Vereinigten Staaten von Amerika. Einen Durchbruch erzielten Steven Rosenberg und seine Kolleg:innen im Jahr 2006 hinsichtlich der Mechanismen der Extraktion, Infiltration und Expansion von Tumorzellen. Die Forschung wurde überwiegend öffentlich finanziert

(über $ 115 Millionen) und bildete die Forschungsgrundlage für die TIL-Therapie an europäischen Zentren, insbesondere dem Netherlands Cancer Institute (NKI) in den Niederlanden.

Das Interesse der Industrie stieg ab 2011, was zur Kooperationsvereinbarung (cooperative research and development agreement, CRADA) zwischen Genesis Biopharma und dem NCI führte. Genesis Biopharma fusionierte 2013 mit Lion Biotechnologies, das Unternehmen wurde 2017 in Iovance Biotherapeutics umbenannt. Nach Abschluss einer strategischen Allianz zwischen Iovance Biotherapeutics und dem University of Texas M.D. Anderson Cancer Center wurden rund $ 14,2 Millionen für die Unterstützung präklinischer und klinischer Forschung bereitgestellt.

Soziale, organisatorische, ethische und rechtliche Aspekte

Mit Lifileucel steht im Falle einer EC-Zulassung eine neue Behandlungsmöglichkeit zur Verfügung, die eine bislang bestehende Versorgungslücke bei der Behandlung erwachsener Patient:innen mit vorbehandeltem inoperablem oder metastasiertem Melanom schließt. Dennoch entstehen Herausforderungen, insbesondere im Bereich der Produktion der Tumor-infiltrierenden Lymphozyten-Zelltherapie sowie bei der Organisation und Ausstattung dafür notwendiger spezialisierter Zentren mit ausreichender Erfahrung (zumindest in CAR T-Zelltherapie) in zellulären Therapien.

Patient:innen mit fortgeschrittenem Melanom berichten von einer eingeschränkten Lebensqualität aufgrund körperlicher (z. B. Symptome im Zusammenhang mit der Entfernung von Lymphknoten, belastende Nebenwirkungen der Immuntherapie) und psychischer Belastungen (z. B. Angst, sowie existenzielle Sorgen). Zudem äußern Patient:innen die Hoffnung, dass Lifileucel nicht nur das Überleben verlängert, sondern auch die Lebensqualität verbessern kann.

Bisher fehlt in Österreich ein spezifisches klinisches Melanom-Register. Relevante Daten sind lediglich über allgemeine Krebsregister verfügbar, wie etwa das österreichische Nationale Krebsregister, das Österreichische Hirntumorregister für Metastasen im zentralen Nervensystem, das Tumorregister Tirol und das Salzburger Krebsregister. Im Gegensatz dazu veröffentlichen in Deutschland zertifizierte Hautkrebszentren jährlich Statistiken zu Melanomen. Auf europäischer Ebene sammelt das Europäische Melanom Register umfassende Daten zu Melanomen.

Weitere Entwicklungen

In drei laufenden klinischen Studien wird Lifileucel bei Patient:innen mit Melanom weiter untersucht. Die Studien werden voraussichtlich im November 2025, März 2028 und August 2029 abgeschlossen. Zwar wurde noch keine HTA für Lifileucel veröffentlicht, doch wird eine Bewertung durch das National Institute of Care and Clinical Excellence (NICE) bis Dezember 2025 erwartet. Außerdem fanden wir insgesamt 16 verschiedene Therapien in der Entwicklung für verschiedene Therapielinien bei inoperablem oder metastasiertem Melanom, darunter auch Next-Generation-TIL-Produkte, die eine höhere Spezifität, Persistenz und Sicherheit und somit eine verbesserte Funktionalität aufweisen.

Schlussfolgerung

Insgesamt stellt Lifileucel eine vielversprechende, aber komplexe therapeutische Option bei Patient:innen mit vorbehandeltem inoperablem oder metastasiertem Melanom dar, die eine sorgfältige Abwägung des klinischen Nutzen-Risiko-Profils erfordert sowie beträchtliche Kosten und erhebliche organisatorische und strukturelle Herausforderungen bei der Implementierung mit sich bringt. Die verfügbare Evidenz zeigt eine klinisch relevante Wirksamkeit bei stark vorbehandelten Patient:innen, je-doch fehlen ein direkter Vergleich zur Immuntherapie, Lebensqualitätserhebungen und es ist noch unklar, ob modifizierte Lymphodepletions-Regime, alternative IL-2-Dosierungen oder andere Begleittherapien das Nebenwirkungsrisiko, ohne Wirksamkeitsverlust, reduzieren könnten. Entscheidungsträger:innen müssen den klinischen Bedarf und das Fehlen von Behandlungsalternativen in der geplanten Indikation sorgfältig gegen die beträchtliche Toxizität – insbesondere infolge der erforderlichen Vor- und Begleittherapie – und die hohen Kosten der neuen Zelltherapie abwägen und dabei die infra-strukturellen Anforderungen, das

zusätzliche Wissen aus laufenden Studien und die öffentlich getätigten Investitionen bei der Therapieentwicklung berücksichtigen.

Executive summary

This health technology assessment (HTA) evaluates lifileucel (AMTAGVI®) for patients with previously treated unresectable or metastatic melanoma.

Disease background

Melanoma is an aggressive form of cancer resulting from the uncontrolled growth of melanocytes, which are cells responsible for producing melanin (pigment that determines skin, hair, and eye colour). Risk factors for melanoma include personal medical history, genetic predisposition, environmental exposure and ultraviolet radiation. The prognosis of melanoma depends on various histologic and clinicopathologic features. In 2023, 27,357 people were living with melanoma in Austria, with approximately 1,845 new diagnoses and roughly 399 deaths in 2022. Information about the distribution of patients amongst stages is available only for a limited number of European countries, but on average, it is estimated that 9% of patients have stage III at diagnosis and 7% have stage IV. Regarding the standard treatments, Austrian clinical experts primarily rely on three guidelines (always the latest versions):

- The European consensus-based interdisciplinary guideline for melanoma
- The European Society for Medical Oncology (ESMO) guideline
- The German S3 guideline (currently being updated)

According to the guidelines, high-risk patients in stage IIB/IIC and patients with operable metastatic disease are treated with adjuvant/neoadjuvant therapy with anti-programmed cell death protein 1 (anti-PD-1) monotherapy or combination immunotherapy in Austria. In case of a BRAF-V600 E/K mutation, adjuvant treatment with dabrafenib/trametinib is an equally effective option in stage III melanoma. The choice of first-line therapy for inoperable metastatic disease depends on previous therapies, the time of the relapse (<6 or ≥6 months after previous therapy) and existing mutations. Checkpoint-inhibitor-based immunotherapies are the treatment of choice, whereby BRAF inhibitors in combination with MEK (mitogen-activated protein kinase-kinase) inhibitors can initially be used as targeted therapy in patients who have already received immunotherapy in the adjuvant/neoadjuvant setting, in the case of BRAF mutation.

Overview of the new medicinal product

Lifileucel is an autologous tumour-infiltrating lymphocyte (TIL) cell therapy that isolates T cells from a patient's tumour tissue, expands them ex vivo, and reinfuses them to generate a personalised anti-tumour response. Lifileucel is administered as a one-time patient-specific intravenous infusion, with each dose containing 7.5×10^9 to 72×10^9 viable cells. Treatment is delivered in an inpatient setting under the supervision of a physician experienced in anticancer therapies and with a particular expertise in cellular therapeutics (e.g. CAR T-cell therapy). Access to intensive care facilities, including the availability of cardiopulmonary and intensive care specialists, is required. Generally, the treatment involves three phases: pre-infusion (multidisciplinary evaluation, tumour resection, and preparative lymphodepletion), infusion (premedication with myeloreductive chemotherapy, lymphodepletion, lifileucel administration, and monitoring), and post-infusion (reassessment, interleukin-2/IL-2 therapy over a 2-week hospital stay).

Lifileucel is currently under evaluation by the European Medicines Agency (EMA), with approval from the European Commission (EC) anticipated in September 2025, with a planned indication for previously treated unresectable or metastatic melanoma in adults. In the US, lifileucel has already been approved by the United States Food and Drug Administration (FDA) in February 2024 for a more detailed indication, namely in patients with unresectable or metastatic melanoma previously treated with PD-1 antibody, and if BRAF V600 mutation positive, with a BRAF inhibitor with or without a MEK inhibitor.

Austrian clinical experts estimate that the number of patients eligible for lifileucel therapy may increase, starting with nine patients in the first year and rising to 27 by the third year after its introduction.

Clinical effectiveness and safety

A phase 2 multicohort, multicentre, open-label, single-arm clinical study evaluated lifileucel in patients with previously treated metastatic or unresectable melanoma. The pooled analysis of two cohorts demonstrated 5% complete response, 26% partial response, and 46% stable disease rates, with an overall objective response rate of 31.4%. Median overall survival was 13.9 months, and progression-free survival was 4.1 months. Additionally, all patients experienced at least one treatment-emergent adverse event, including thrombocytopenia (76.9%), anaemia (50.0%) and febrile neutropenia (41.7%). Six patients died within 30 days after lifileucel infusion, of which four were deemed to be treatment related but mainly due to necessary lymphodepletion and IL-2 therapy.

The European Society for Medical Oncology (ESMO) rated lifileucel with a Magnitude of Clinical Benefit Scale (MCBS) score of 2/5 due to toxicity concerns, indicating no substantial clinical benefit. Critically, no quality-of-life data are available. The study's methodological quality was assessed as moderate because of an open-label design, lack of a comparator and the inappropriateness of retrospective pooling of the cohorts. The certainty of evidence with GRADE was assessed as low to very low.

Economic aspects

Lifileucel has no set price in Europe yet. The pharmaceutical company reported the US wholesale acquisition cost (WAC) of $562,000, which was converted to €506,000. The manufacturer calculated a rough budget impact of lifileucel around €5 to €10 million annually. However, the analysis was not based on Austrian data.

Based on our calculations for the Austrian context before price negotiation, with necessary additional treatments, the direct medical costs for lifileucel amount to around €9.1 million annually, resulting in around €27.3 million over three years for an estimated population of 17 patients per year. Considering also the costs of the SoC for the patients who are not eligible for lifileucel, the lifileucel scenario results in total costs of €14.6 million per year and €43.8 million for years 1–3. In comparison, the SoC scenario without lifileucel costs around €6.8 million annually and €20.4 million over three years for an estimated population of 87 patients.

Public investment aspect

The development of lifileucel for nonresectable melanoma began at the National Cancer Institute (NCI) in the United States in the late 1990s. This research was primarily publicly funded (over $115 million) and laid the foundation for TIL therapy, which was later adopted and further developed by European centres, notably the NCI. Industry interest increased in 2011. Genesis Biopharma subsequently merged with Lion Biotechnologies in 2013, and the company was renamed Iovance Biotherapeutics in 2017. After signing a strategic alliance agreement between Iovance Biotherapeutics and the University of Texas M.D. Anderson Cancer Center, around $14.2 million was allocated to support preclinical and clinical research under the collaboration.

Social, organisational, ethical and legal aspects

Lifileucel addresses an unmet clinical need for patients with previously treated unresectable or metastatic melanoma. However, challenges remain, including technical issues related to manufacturing TIL therapies and organisational difficulties, such as providing appropriately equipped centres with trained staff, ensuring timely and efficient planning, coordinating shipping logistics, and providing multidisciplinary support. Furthermore, Austrian clinicians are concerned about worsening the existing hospital personnel and structural resource problems, particularly in cell therapy units, which already have to handle the continuous increase of CAR T-cell therapies.

From a patient perspective, two surveyed patients (of note, neither of the two received lifileucel) reported reduced quality of life due to physical symptoms (e.g., symptoms related to lymph node removal, burdensome adverse events from immunotherapy) and mental health challenges (e.g., anxiety, fear, existential

concerns). They also expressed hope that new therapies will not only extend life but also improve their quality of life.

So far, there is no dedicated clinical Austrian melanoma registry. Data are only available through general cancer registries. In contrast, Germany maintains detailed statistics through annual reports of public skin cancer centres. At the European level, the European Melanoma Registry collects comprehensive data on melanoma and other types of skin cancer.

Landscape overview

Lifileucel is being further investigated in three ongoing clinical trials in patients with melanoma. The trials are expected to be completed in November 2025, March 2028 and August 2029. Although an HTA for lifileucel has not yet been published, an assessment by the National Institute of Care and Clinical Excellence (NICE) is expected by December 2025. We also found a total of 16 different therapies in development for different lines of therapy for inoperable or metastatic melanoma, including next-generation TIL products that show higher specificity, persistence and safety, and thus improved functionality.

Conclusion

Overall, lifileucel is a promising but complex therapeutic option for patients with previously treated unresectable or metastatic melanoma, which requires careful consideration of the clinical risk-benefit profile and entails considerable costs and significant organisational and structural challenges during implementation. The available evidence shows clinically relevant efficacy in heavily pretreated patients, but there is a lack of direct comparison to immunotherapy, quality of life data, and it is still unclear whether modified lymphodepletion regimens, alternative IL-2 doses or other adjunctive therapies could reduce the risk of side effects without a loss of efficacy. Thus, decision-makers need to carefully weigh the clinical need and lack of treatment alternatives in the planned indication against the considerable toxicity – particularly because of the required pre- and concomitant therapy – and the high costs of the new cell therapy, taking into account the infrastructural requirements, the additional knowledge from ongoing studies and the public investment in therapy development.

1 Introduction

The objective of this report is to evaluate the clinical effectiveness and safety as well as the economic and organisational aspects of lifileucel (AMTAGVI®), a tumour-derived autologous T-cell immunotherapy, for previously treated adult patients with unresectable or metastatic melanoma.

Lifileucel zur Behandlung von Erwachsenen mit inoperablem oder met. Melanom

1.1 Disease background

Overview

Melanoma represents an aggressive form of cancer characterised by uncontrolled growth of melanocytes [1], specialised cells responsible for producing melanin, the pigment that determines the colour of skin, hair, and eyes [2]. Generally, the term "melanoma" refers to cutaneous melanoma and its subtypes, as melanocytes are primarily located in the skin (90% of primary melanomas originate from the skin) [3]. Since melanocytes are also found in other regions of the body, melanomas can also develop in mucous membranes (mucosal melanoma) or the eyes (uveal melanoma) [4].

kutanes Melanom: aggressiver Hautkrebs, entsteht durch unkontrolliertes Wachstum von Melanozyten

Melanoma develops when melanocytes undergo malignant transformation due to genetic alterations (e.g., mutations, deletions, translocations) and epigenetic changes, including micro ribonucleic acid (microRNA) expression and deoxyribonucleic acid (DNA) methylation, that disrupt normal cellular regulation [1]. There are various risk factors associated with the development of melanoma, including personal medical history, genetic predisposition, environmental exposure, and ultraviolet (UV) radiation [5-7]. The main risk factors are shown in Figure 1-1 in the Appendix.

Risikofaktoren: gen. Veranlagung, pers. Vorgeschichte, Umwelt- & UV-Exposition

Classification

Traditional morphological classification identifies four main subtypes of cutaneous melanoma: superficial spreading melanoma (70% of melanomas), nodular melanoma (15–30%), lentigo maligna melanoma (10–15%), and acral lentiginous melanoma (<5%) [8]. The clinical manifestation differs between the four subtypes, with the associated features listed in Chapter 1 in the Appendix. Although the subtype classification can be important for histopathologic recognition and diagnosis, it does not provide information about the biologic behaviour of the tumour, nor does it inform the management of advanced disease [9].

morph. Unterteilung in 4 Haupttypen

The current taxonomy of melanoma is influenced by [8]:

- Site of origin (epithelium-associated vs non-epithelium-associated),
- Role of cumulative sun damage (CSD; high CSD-related, low CSD-related, or non-CSD-related),
- Mole phenotype (high vs low nevus count),
- Frequency of following mutations: BRAF, neuroblastoma rat sarcoma viral oncogene homologue (NRAS), neurofibromin 1 (NF1), KIT (stem-cell factor receptor, CD117).

Einflussfaktoren auf die Melanom-Klassifikation:

ursprüngliche Lokalisation, Ausmaß UV-Schädigung, Muttermal-Phänotyp, mol. Mutation

Stages and clinical manifestations

Krankheitsverlauf in 5 klin. Stadien nach TNM-Klassifikation (Tumor, Lymphknoten, Metastasen)

Melanoma follows a progressive disease course characterised by distinct clinical stages. The American Joint Committee on Cancer (AJCC) has developed an internationally recognised staging system, which classifies cancer based on three factors: tumour (T), regional lymph node involvement (N), and distant metastasis (M) [10]. This standardised framework stratifies the disease into stages 0 (melanoma in situ) through IV.

Stadien 0–4

Stage 0 denotes in-situ melanoma, where the tumour is still growing along the basal layer of the epidermis and the basement membrane is still intact. In stage I, malignant melanocytes have entered the upper dermal layer. In stage II disease, the tumour extends to deeper dermal layers or subcutaneous fat. As tumour thickness and ulceration of the overlying epidermis are the most important factors predicting the risk of metastasis, stage II is further divided into stage IIA–IIC based on these factors. After reaching larger blood and lymphatic vessels, melanoma can spread to locoregional lymph nodes or metastasise within the adjacent skin (stage III). In stage IV, the cancer has spread beyond the locoregional lymph nodes into distant parts of the body [11]. A visual representation of the five stages is shown in Figure 1-1 below.

fortgeschr. Melanom: Ausbreitung über den Primärherd hinaus

klin. Manifestation: abh. von Lokalisation der Fernmetastasen

Advanced melanoma has spread beyond the primary site, including disease stage III (when regional lymph nodes are involved or in-transit metastases are present), and disease stage IV (with distant metastases to organs, distant lymph nodes, or skin) [10]. The clinical presentation of melanoma varies significantly depending on disease stage and extent of the spread. Tumours can metastasise to the lungs, brain, bones, or liver, causing organ-specific symptoms such as breathing difficulties, neurological deficits, bone pain, or liver dysfunction [12].

Refer to Chapter 1 in the Appendix for a detailed presentation of the TNM criteria and further information about stages III-IV.

Diagnosis

Diagnostik im met. Stadium:

PET/CT als Goldstandard,

MRT für Hirnmet.-Detektion,

Tumormarker S100B/LDH als Prognosefaktoren,

mol. Testung auf Mut.

In addition to general diagnostic procedures for melanoma, the diagnostic workup for unresectable and metastatic melanoma includes comprehensive cross-sectional imaging, with positron emission tomography (PET)/computed tomography (CT) as the gold standard due to superior diagnostic accuracy or a contrast-enhanced CT. A brain MRI provides optimal detection of cerebral metastases. Supplementary modalities include abdominal and lymph node ultrasound and skeletal scintigraphy if bone lesions cannot be accurately assessed by CT or magnetic resonance imaging (MRI). Laboratory assessment requires tumour markers S100 calcium binding protein B (S100B) and lactate dehydrogenase (LDH), essential prognostic factors that correlate with disease stage. Molecular diagnostics from stage IIIB onward include testing for BRAF mutations (~50% of melanomas), NRAS mutations in BRAF-wildtype cases (~15%), and c-KIT mutations in acral and mucosal subtypes (~5%) [13].

Prognosis

5-Jahres-Überlebensrate bei met. Melanom (Stadium IV): 34,6 %

The prognosis of melanoma depends on several histologic and clinicopathologic features [14]. The 5-year relative survival rate for patients with cancer that has spread to regional lymph nodes (stage III) is 75.7%, and the 5-year relative survival rate for patients with metastasised cancer (stage IV) is 34.6% [7].

Epidemiology

in Ö:
Prävalenz: 27.357 Pat.,
Inzidenz: 1.845 Pat./Jahr;
Mortalität: 399 Pat./Jahr;

According to Statistik Austria, 27,357 people were living with melanoma in Austria in 2023 [15]. In 2022, there were approximately 1,845 new diagnoses (19.7 cases per 100,000) and roughly 399 deaths that year (4.2 deaths per 100,000 persons) [16]. However, the data from Statistik Austria underestimate the real burden of melanoma in Austria, as they only report cases treated within the public hospital system [17]. The overall uncertainty of the population estimates represents one of the limitations of the budget impact analysis (see chapter 5.3.1).

keine publ. Daten zur Stadien-Verteilung

gesch. Pat. (in %):
Stadium III: 9 %
Stadium IV: 7 %

Lifileucel is indicated for patients with advanced (unresectable or metastatic) melanoma, i.e. patients in stage IV and some cases in stage III that cannot be surgically removed. However, Statistik Austria does not publish a sufficiently detailed distribution of melanoma stages at diagnosis. Information about the distribution of patients amongst stages is available only for a limited number of European countries, but on average, it is estimated that 9% of patients have stage III at diagnosis [18]. For detailed distribution of melanoma substages according to the AJCC 8th edition, a population-based registry study classified 55% of stage III patients under substage IIIC and 3% under substage IIID [19]. Patients with stage IV represent 7% of melanoma incidence in Austria ("disseminated stage") [16].

1.2 Standard of care in Austria

laut ö. Exp.:
Orientierung hauptsächlich an eur. Leitlinien

According to Austrian clinical experts, the treatment of advanced (unresectable or metastatic) melanoma[1] is primarily based on the following two guidelines:

- The European consensus-based interdisciplinary guideline for melanoma [24]
- The European Society for Medical Oncology (ESMO) guideline [25].

weitere Leitlinien werden bei Bedarf herangezogen

Furthermore, the German S3 guideline [13] also represents a primary reference source; however, it is currently in the process of being updated (latest version: 2020) [26]. Additionally, the American National Comprehensive Cancer Network (NCCN) guideline is occasionally consulted as a supplementary resource [22].

trotz therap. Fortschritts, bedeutende klin. Herausforderung

Although significant progress has been made in treating unresectable or metastatic melanoma, particularly with the introduction of immunotherapy, which has improved patient outcomes, many patients still experience disease recurrence or progression [28].

[1] The therapy of non-cutaneous melanomas may deviate from the guidelines. For further information on these rare types, European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) provide separate guidelines [20-23]. The S3-Guideline directly incorporates recommendations for non-cutaneous melanoma types within the document [13].

Figure 1-1 shows the treatment algorithm, according to identified guidelines for the proposed indication of "treatment of adult patients with unresectable or metastatic melanoma previously treated with an anti-PD-1 (anti-programmed cell death protein 1), and if BRAF V600 positive, a BRAF inhibitor with or without a MEK (mitogen-activated protein kinase kinase) inhibitor, in the adjuvant/neoadjuvant setting. The choice of subsequent treatment is based on the timing of relapse after therapy (<6 or ≥6 months after completion), depending on previous therapies received and the presence of a BRAF mutation or BRAF wild-type status [24].

bei Therapieprogression indiv. Zweitlinientherapien je nach Zeitpunkt des Rückfalls und Vorliegen einer BRAF-Mutation

For immunotherapeutic approaches, the SoC with a marked preference is the combination regimen of nivolumab (NIVO, four cycles) plus ipilimumab (IPI, four cycles), which constitutes approximately 80% of cases, while NIVO (three cycles) plus anti-lymphocyte-activation gene 3 (anti-LAG-3) inhibitor relatlimab (three cycles) combination accounts for the remaining 20% of therapeutic interventions [26]. For further information on the therapies and their dosages (used in Austria), see Appendix Chapter 1.

klin. Praxis in Ö:
Nivolumab + Ipilimumab
oder
Nivolumab + Relatlimab
bei BRAF-Wildtyp

For BRAF-mutated melanoma previously exposed to PD-1 inhibitors treatment with a combination therapy of a BRAF inhibitor and a MEK inhibitor (until no effectiveness or toxicity) like dabrafenib combined with trametinib or encorafenib combined with binimetinib can be given before using a combination immunotherapy.

Dabrafenib + Trametinib
oder
Encorafenib + Binimetinib
bei BRAF-Mutation

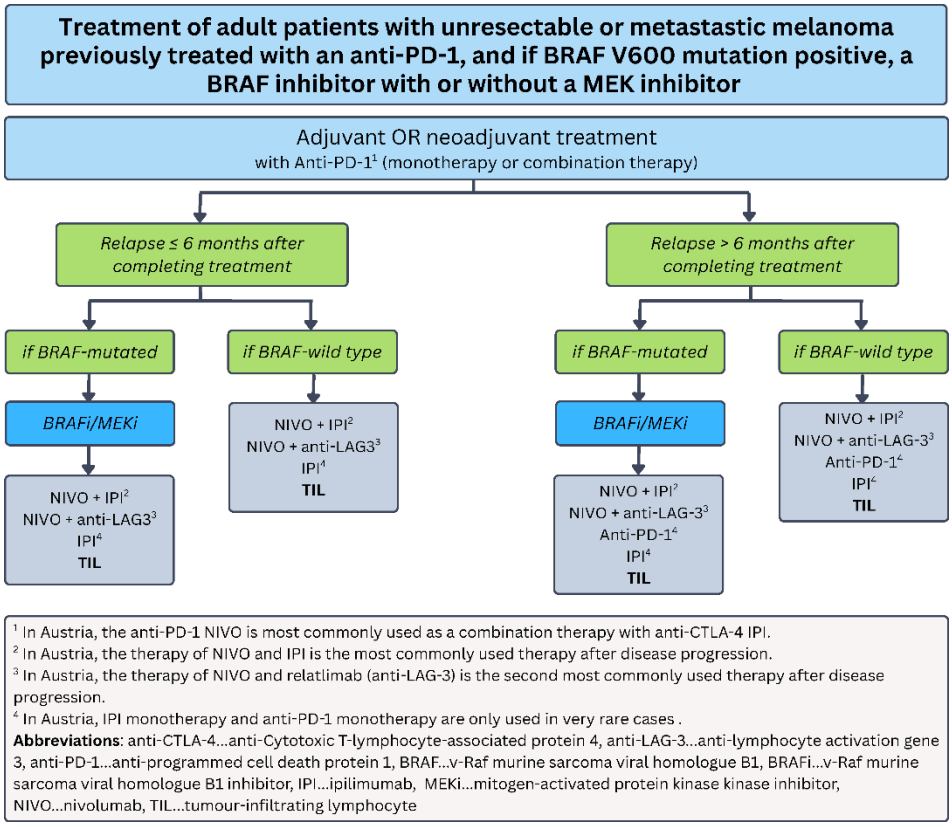


Figure 1-1: Treatment algorithm for the proposed indication: the treatment of patients with unresectable or metastatic melanoma previously treated with an anti-PD-1, and if BRAF-V600 positive, a BRAF inhibitor with or without a MEK inhibitor (Adapted from [24] and coordinated with Austrian clinicians [26])

Follow-up

The follow-up schedule for patients with advanced melanoma should be tailored to each patient individually, considering disease stage, individual risk of recurrence and personal needs of the patient. Figure 1-2 shows the algorithm proposed by the ESMO, for the follow-up of melanoma stage IIB to stage IV patients [25].

indiv. Nachsorge abh. vom Stadium, Rückfallrisiko und pers. Bedürfnis

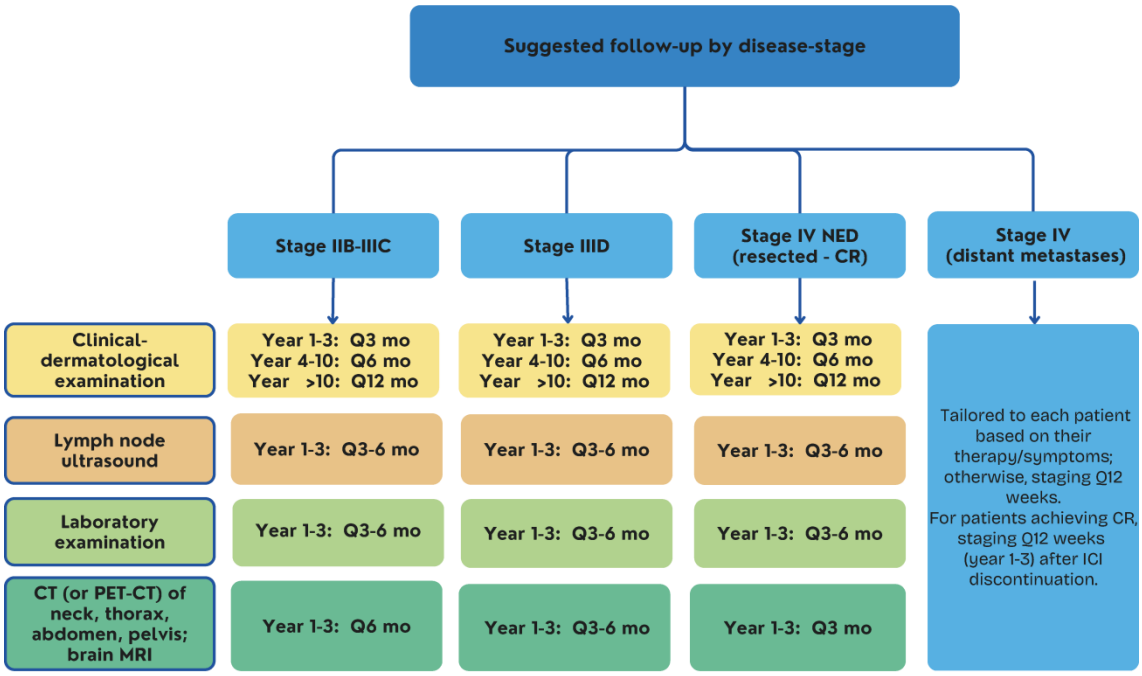


Figure 1-2: Proposed algorithm for the follow-up of patients with advanced melanoma. Adapted from [25].

1.3 Medicinal product under evaluation

The medicinal product under evaluation in this health technology assessment (HTA) is lifileucel (AMTAGVI®), the first in class autologous tumour-derived cell therapy [12, 29]. Table 1-1 summarises the most important information about this product.

HTA-Bericht zu Lifileucel (AMTAGVI®): autologe T-Zell-Immuntherapie

Table 1-1: Characteristics of the medicinal product [30]

INN	Lifileucel
Product name	AMTAGVI®
Active substance(s)	Lifileucel
Anatomical Therapeutic Code	L01XL11
Pharmacologic class	Antineoplastic agents
Manufacturer/MAH	Iovance Biotherapeutics

Abbreviations: INN … International non-proprietary name, MAH … marketing authorisation holder

The autologous tumour-infiltrating lymphocyte (TIL) cell therapy is based on the isolation, ex vivo expansion, and reinfusion of T cells from the tumour tissue recognises melanoma antigens and produces a specific anti-melanoma immune response [31].

Wirkmechanismus: Pat.-indiv. T-Zellen vermitteln eine Antitumorreaktion

Regulatory status

Lifileucel is currently under evaluation by the European Medicines Agency (EMA). The manufacturer submitted the marketing authorisation application (MAA) in August 2024. Decisions from the Committee for Human Medicinal Products (CHMP) are expected in July 2024, and from the European Commission (EC) in September 2025 [30]. The planned indication is "previously treated unresectable or metastatic melanoma in adults" [32]. Table 1-2 provides EMA regulatory information on lifileucel.

Antrag auf EMA-Zulassung vom Hersteller im August 2024 eingereicht

Table 1-2: EMA regulatory information on lifileucel (AMTAGVI®) [32]

Orphan medicinal product	No
Conditional marketing authorisation	No
Specific obligations of the conditional marketing authorisation	Yes
Additional monitoring	No
Accelerated approval	No
Exceptional circumstances	No
ATMP	Yes
PRIME	No
First approved indication	Not approved
Details of ongoing early access programmes in the EU (as provided by the MAH)[a]	No named patient programmes planned in Austria (May 2025)

Abbreviations: ATMP … Advanced Therapy Medicinal Product, EU … European Union, MAH … Marketing Authorisation Holder, PRIME … Priority Medicines

Notes: [a] for further details on ongoing early access programs, please refer to the submission dossier.

The regulatory status in other countries ranges from accelerated to no approval. Lifileucel received accelerated biologics license application (BLA) approval by the United States Food and Drug Administration (FDA) on 16 February 2024 [33]. The complete prescribing information approved by the FDA indicates lifileucel for "the treatment of patients with unresectable or metastatic melanoma previously treated with programmed cell death protein 1 (PD-1) blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor" [33]. In addition, the marketing authorisation holder (MAH) plans to submit to regulatory authorities in Australia (Therapeutic Goods Administration, TGA) and Switzerland (Swissmedic) and has already applied to regulatory bodies in Canada (Health Canada) and the United Kingdom (UK, Medicines and Healthcare products Regulatory Agency, MHRA) [34].

internationale Zulassungen:

USA: FDA-Zulassung seit 16.02.2024

geplant (Schweiz, Australien) und beantragt (Kanada, UK)

Posology

For manufacturing lifileucel, tumour tissue is procured from the patient and sent to the manufacturing facility to generate the final product for infusion [35]. The total manufacturing time is around 33 days (from receipt of the tumour tissue in the manufacturing centre until shipment-ready lifileucel). The long production time of lifileucel must be considered when selecting

Produktionsdauer von Lifileucel ~ 33 Tage

patients for this therapy as patients may experience disease progression within this time period [31].

Lifileucel, the finished product, is stored in patient-specific infusion bags (one to four, with protective metal cassettes) [31]; the product is thawed before one-time intravenous (IV) administration back into the same patient [12]. Each bag contains 7.5 x 10^9 to 72 x 10^9 viable cells for infusion [33]. The administration of lifileucel should be performed in an inpatient hospital setting under the supervision of a physician experienced in the use of anticancer agents. Furthermore, access to an intensive care unit is required [26]. Figure 1-3 gives an overview of the treatment with lifileucel.

einmalige Pat.-indiv. intravenöse Gabe: 1 Infusion mit 7,5 x 10^9 bis 72 x 10^9 lebenden Zellen

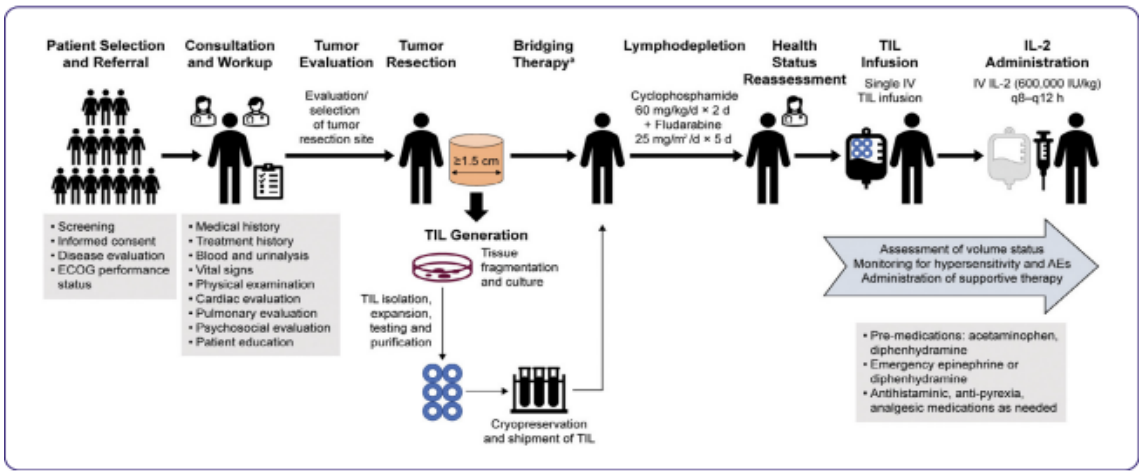


Figure 1-3: TIL therapy overview [36]

Abbreviations: AE … adverse event, ECOG … Eastern Cooperative Oncology Group, IL-2 … interleukin-2, IV … intravenous, TIL … tumour-infiltrating lymphocyte, q … every.

Note: [a]administered as needed.

Requirements for companion diagnostics and/or monitoring

The administration of lifileucel involves three treatment phases: before, during, and after the infusion.

- **Before lifileucel infusion:**
  - *Patient and tumour evaluation:* Patients require an adequate performance status (ECOG 0–1), including cardiac (EF >50%), pulmonary, and renal functions (GFR >60ml/min/1,73m^3), to be suitable for the treatment with lifileucel. Furthermore, it requires multidisciplinary care, and patients should be referred to an authorised treatment centre (ATC), defined as a cellular therapy unit with experience in at least CAR T-cell therapies [35].
  - *Tumour resection:* For manufacturing lifileucel, at least 1.5cm of tumour tissue is required [35], which is then shipped in a hypothermosol solution to the manufacturing site [12].
  - *Shipping logistics:* A collaboration among ATC, the courier, the laboratory, and the manufacturer is necessary. The treatment involves two supply chains: the transport of tumour tissue to the manufacturer and the transport of lifileucel to the ATC. The tumour tissue should be stored at 2–8°C until transportation [35].

VOR der Infusion:

Evaluierung d. Pat./Tumor, multidisziplinäre Versorgung in spez. Zentren, …

… Tumorresektion: mind. 1,5 cm Gewebe notwendig,

Transportlogistik (Tumorgewebe & Produkt)

- *Bridging therapy:* Patients may require bridging regimens during tumour manufacturing, ranging from BRAF or MEK inhibitors, immune checkpoint inhibitors (ICIs) to chemotherapy [36].
- *Preparative lymphodepleting chemotherapy:* The nonmyeloablative lymphodepletion regimen includes cyclophosphamide 60mg/kg/d for two days, then fludarabine 25mg/m^2/day for five days [38].

überbrückende Therapie

konditionierende Therapie & Chemo (Lymphodepletion)

- **In addition to the lifileucel infusion:**
  - 30 to 60 minutes before lifileucel infusion, patients receive acetaminophen and diphenhydramine or another histamine 1 receptor (H1)-antihistamine [29].
  - The infusion also contains Plasma-Lyte A, human serum albumin, interleukin-2 (IL-2), and small quantities of antibiotics (gentamicin, streptomycin, and aminoglycoside antibiotics) [36].
  - Patients are admitted to the hospital and monitored for treatment-emergent adverse events (TEAEs) [36].

ZUSÄTZLICH zur Infusion:

Prämedikation; Monitoring von Infusionsreaktionen

- **After lifileucel infusion:**
  - The health status of the patient is reassessed before applying IL-2 [36].
  - IL-2 is started with 600,000 IU/kg three to 24 hours after lifileucel. It is administered intravenously every eight to 12 hours and up to six times [38]. The administration should be scheduled around optimal staffing times (ideally) [36].
  - During the administration of IL-2, patients are admitted to the hospital (for around two weeks after lifileucel infusion) [35].
  - Patients are monitored during IL-2 to manage IL-2 toxicities (adverse events, AEs) [36].
  - After hospital discharge, patients should remain close to the ATC (around 45–80 kilometres or <1 hour) up to 30 days after receiving lifileucel [36].

NACH der Infusion:

erneute Untersuchung vor IL-2 Gabe, ...

... 2-wöchiger Krankenhausaufenthalt für IL-2 Gabe

nach Entlassung: Nähe zu spez. Zentren für 30 Tage empfohlen

Use in specific populations

- *Patients with adrenal insufficiency or hypophysitis:* They may need additional fluids to manage hypotension. They should continue physiological replacement steroids (<10mg prednisone or equivalent) during treatment, and stress-dose steroids should only be administered after consulting an endocrinologist [35].
- *Patients with brain metastases:* An ongoing clinical trial evaluates the feasibility and safety of lifileucel for patients with untreated or actively growing brain metastases. Outside of clinical trials, surgery or radiation therapy is recommended before treatment with lifileucel [35].
- *Patients with potential vulnerabilities:* There is insufficient information on the safety and efficacy of lifileucel in elderly, paediatric, pregnant, and breastfeeding patients. No differences in terms of safety and effectiveness were reported between elderly patients (≥65 years) and younger patients. However, according to the package insert, lifileucel is not recommended for pregnant and/or breastfeeding persons [29].

Anwendungen bei Pat. mit Nebenniereninsuffizienz, Hypophysitis & Hirnmetastasen: grundsätzlich empfohlen, umfassende Abwägungen notwendig

keine Daten zur Anwendung bei Schwangeren oder stillenden Personen: nicht empfohlen

Expected number of patients receiving lifileucel in Austria

According to Austrian clinical experts, the number of eligible adult patients with previously treated unresectable or metastatic melanoma for lifileucel therapy might increase over the years, assuming nine (10%) patients in the first year, 18 (20%) in the second year and 27 (30%) in the third year after the introduction of lifileucel [40].

Pat.-Anzahl, die für Lifileucel in Frage kommen:
ca. 9–27 Pat. in Jahr 1–3 (laut öst. Expert:innen)

2 Scope of assessment

This report aims to evaluate the clinical effectiveness, safety, and economic and other aspects of lifileucel (AMTAGVI®) for previously treated adult patients with unresectable or metastatic melanoma.

HTA: Evaluierung von Lifileucel bei inoperablem, metastasiertem Melanom

2.1 Research questions

The following research questions will be answered in the present report:

1. **Clinical domain:**

   In adult patients with unresectable or metastatic melanoma who have previously received treatment with a programmed cell death protein 1(PD-1) blocking antibody and if BRAF V600 mutation-positive, a BRAF inhibitor with or without a mitogen-activated protein kinase inhibitor (MEKi), is lifileucel more effective and safer compared to the current standard treatment in Austria in terms of patient-relevant outcomes?

   klin. Domäne: Wirksamkeit und Sicherheit

2. **Non-clinical domains:**

   What are the economic, ethical, organisational and social consequences of implementing lifileucel into the Austrian healthcare system?

   What were the key contributions of publicly funded research institutions and private companies in discovering and developing lifileucel as a therapy for pretreated patients with unresectable or metastatic melanoma, and how did the transfer of intellectual property rights impact the therapy's advancement through clinical trials to market authorisation?

   nicht-klin. Domänen: ökonomisch, ethisch, organisatorisch, soziale Konsequenzen, sowie öffentliche Beiträge zu Entwicklungskosten

2.2 Inclusion criteria

Inclusion criteria for relevant clinical studies are summarised in Table 2-1.

Einschlusskriterien für relevante klin. Studien

Regarding the non-clinical domains, relevant economic literature was included with information about lifileucel prices, other direct medical costs and health economic evaluations. In addition, relevant literature for the organisational, ethical and social domain, as well as literature on public investment, such as information on public grants, funding and contributions, was considered.

zusätzlich Literatur für nicht klin. Bereiche berücksichtigt

Table 2-1: Assessment scope, including the patient, intervention, comparison and outcome (PICO) question for the clinical domain

PICO	Description of PICO elements
P	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.
I	Lifileucel (AMTAGVI®), Iovance Biotherapeutics
C	Treatment after first-line neo-(adjuvant) treatment with IPI+NIVO (only neo-adjuvant) OR anti-PD-1 (pembrolizumab neo-adjuvant + adjuvant and NIVO or pembrolizumab adjuvant alone) or if BRAF-mutated, second line BRAF/MEK inhibitor (dabrafenib, encorafenib, vemurafenib/binimetinib, cobimetinib, trametinib): ■ Relapse on treatment or ≤6 months after completing treatment: BRAF-wild type second-line OR BRAF-mutated third-line: NIVO+IPI OR NIVO+anti-LAG3 OR IPI ■ Relapse ≥ 6 months after completing treatment: BRAF-wild type second-line OR BRAF-mutated third-line: NIVO+IPI OR NIVO+anti-LAG3 OR anti-PD-1 OR IPI
O	Efficacy: ■ OS ■ ORR ■ PFS ■ DOR PROs: ■ HRQoL Safety: ■ Toxicities ■ AEs ■ SAEs ■ TEAEs ■ Death
Studies	■ Randomised controlled trials ■ Non-randomised controlled trials ■ Observational and single-arm studies (n≥40)
Languages	English and German

Abbreviations: AEs … adverse events, anti-LAG3 … lymphocyte-activation gene 3, anti-PD-1 … programmed cell death protein 1, DOR … duration of response, HRQoL … health-related quality of life, IPI … ipilimumab, MEK … mitogen-activated protein kinase kinase, n … number of patients, NIVO … nivolumab, ORR … objective response rate, OS … overall survival, PFS … progression-free survival, SAEs … serious adverse events, TEAEs … treatment-emergent adverse events

Note: outcomes in bold *indicate critical efficacy and safety endpoints based on clinical expert consultation.*

3 Methods

The methods section of this report outlines a comprehensive approach for multiple domains. The overall data cut-off of the report was 22 May 2025, after the pharmaceutical company sent the dossier.

multimethod. Ansatz: Daten cut-off: 22.05.2025

Systematic literature search and study selection

A systematic literature search was conducted on 7 May 2025, across four databases: Medline via Ovid, Embase, The Cochrane Library, and INAHTA. The search was limited to English and German sources, excluding conference abstracts (see detailed search strategies in Chapter 3 in the Appendix). After deduplication, 495 citations were identified. Additional searches in three clinical trial registries (ClinicalTrials.gov, WHO-ICTRP, EU Clinical Trials) yielded 256 potentially relevant hits. The manufacturer also submitted a dossier on 22 May 2025; however, no new citations were identified from this source.

1 systematische Literatursuche in vier Datenbanken: 495 Treffer; & Suche nach laufenden Studien: 265 Treffer

Hersteller: übermitteltes Dossier am 22.05.2025

The study selection process followed a structured approach, where two researchers independently screened references at the abstract level. Similarly, selected full texts were screened independently, with arbitration by a third researcher when disagreements arose. One study and the manufacturer dossier were ultimately included for clinical qualitative synthesis, while four studies were selected for the informative chapter on other tumour-infiltrating lymphocytes (TIL). Eighteen additional references were chosen for non-clinical domains. The study selection process is presented as a preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram in Chapter 3 in the Appendix.

Literaturauswahl: klinische Domäne (n=1 + Herstellerdossier), nicht-klin. Domäne (n=18)

Clinical effectiveness and safety assessment

For the clinical effectiveness and safety assessment, the study quality for uncontrolled trials was evaluated using the Institute of Health Economics (IHE) checklist [41]. Data extraction was systematically performed by one reviewer and cross-checked by a second reviewer with consensus resolution.

Bewertung der Studienqualität im 4-Augenprinzip mit der IHE-Checklist

In addition, European Society For Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) score evaluation has been extracted from the scorecard [44].

The strength of evidence was rated individually according to the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) scheme for each critical endpoint. Each study was rated by two independent researchers. In case of disagreement, a third researcher was involved to resolve the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [45].

GRADE Framework für Einschätzung der Vertrauenswürdigkeit der Evidenz

GRADE uses four categories to rank the strength of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;

- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

Economic evaluation methods

Price information was collected by the Austrian National Public Health Institute (Gesundheit Österreich GmbH, GÖG).

Preisinfo von GÖG

We performed additional manual searches in the Google search engine and the PubMed database to identify existing economic evaluations that evaluated lifileucel or TIL as the intervention.

weitere manuelle Suchen nach ökonomischen Analysen zu Lifileucel/TIL

Furthermore, we conducted a budget impact analysis (BIA) that incorporated several approaches:

Budgetfolgenanalyse: ...

- A placeholder price of €506,000 per single infusion of lifileucel was established for BIA based on converted US wholesale acquisition cost (WAC) pricing.

... US-Platzhalterpreis

- Patient population estimates were derived from published epidemiological data, complemented by clinical estimates from other countries (Sweden, Slovakia) and validated by Austrian clinical experts.

... Pat. epid. Daten von Schweden und Slowakei + Exp.-Info

- Cost calculations incorporated outpatient sector prices from the Austrian refund code (Erstattungskodex, EKO) and inpatient treatment costs from diagnosis-related group data (Leistungsorientierte Krankenanstaltenfinanzierung, LKF). The unit costs are listed in Chapter 5 in the Appendix.

... Kostendaten vom EKO- (niedergelassen) bzw. LKF-Katalog (krankenhausbezogen)

- Dosages for calculating the total treatment costs are presented in Chapter 1 in the Appendix.

... 3-Jahres-Zeithorizont

- According to the implementing regulation §4 (2), a three-year BIA included gross drug budget impact, net drug budget impact (including cost offsets), and additional costs related to administration.

... Lifileucel- vs. Standardtherapieszenarien für Pat. mit inoperablem bzw. met. Melanom

- The analysis presents treatment scenarios for unresectable or metastatic melanoma patients (stage IIIC-IV). In the intervention scenario with the new drug, lifileucel retreatment is not foreseen and all the patients indicated for the treatment will receive complete treatment. Minor cost categories and additional treatments were excluded from the analysis. In modelling the change in the treatment mix after lifileucel reimbursement in the primary analysis, we assumed that the indicated population would remain stable over the years and lifileucel will take 20% market share from the comparators in proportion to their current estimated distribution. In the scenario analysis, we assumed steadily increasing market penetration (10%–20%–30%) and a concomitant 2% annual increase in the advanced melanoma incidence.

... primäre Analyse: Lifileucel 20 %-Marktanteil in Jahr 1–3

... Szenarioanalyse: steigender Markanteil zw. 10 % & 30 %

Organisational, ethical and social assessment

The organisational, ethical, and social assessment utilised the European Network for Health Technology Assessment (EUnetHTA) Core Model®. Data were gathered from three sources:

organisatorische Aspekte nach dem EUnetHTA CoreModel® – 3 Quellen:

- Structured patient questionnaires were completed by two female patients with malignant melanoma stage IV (see Chapter 6 in the Appendix for details).
- Expert consultations with five leading clinicians (see Chapter 6 in the Appendix).

Exp.-Konsultationen, schriftliche Pat.-Befragungen & Literaturquellen

- Systematic literature review and manual search findings.

Development costs and public contributions

The methodology for assessing development costs and public contributions involved several steps (see Chapter 7 in the Appendix for details):

- Identifying product origins through searches for generic/non-proprietary names and trade names.
- Searching for the earliest references to identify basic R&D support and research grants.
- Exploring databases on clinical trials and research funding.
- Examining company websites for information on funding rounds, sponsors, mergers, and acquisitions.
- Searching SEC reports for information on acquisitions, patents and shareholders.
- Reviewing business news sources for additional information.

Additionally, we compiled a landscape overview of other therapies, which are in the development for second-line and later treatment of unresectable or metastatic melanoma, using the International Horizon Scanning Initiative (IHSI) database [46], supplemented by a review of other TIL products in the pipeline identified through current literature.

Entwicklungskosten und öffentliche Beiträge erhoben: ...

... Identifizierung von generischen oder (nicht) geschützten Bezeichnungen

... Produktherkunft & Grundlagenforschung

... Finanzierungsrunden, Fusionen & Übernahmen zusätzlicher Überblick zu anderen Therapien in Entwicklung und TIL-Produkten

4 Clinical effectiveness and safety

4.1 Characteristics of included studies

One phase 2, interventional, open-label, non-randomised clinical study (C-144-01) with parallel assignment to four arms comprising Cohorts 1 to 4 was identified:

1 klin. Phase-2 Studie mit 4 Kohorten

- *Cohort 1:* Patients infused with non-cryopreserved lifileucel product.
- *Cohort 2:* Patients infused with cryopreserved lifileucel product.
- *Cohort 3:* Patients previously treated in cohort 1, cohort 2, or cohort 4 had progressed and opted to be rescreened and retreated with the lifileucel regimen, using cryopreserved lifileucel product.
- *Cohort 4:* Patients infused with cryopreserved lifileucel product.

Kohorte 2 und 4 erhielten gefrorenes Lifileucel

Kohorte 3: Pat. aus Kohorte 1, 2 und 4, die eine weitere Dosis erhielten

The non-cryopreserved product infused in cohort 1 is no longer in clinical use. cohorts 2, 3, and 4 used the same manufacturing process to generate cryopreserved lifileucel product.

gleicher Herstellungsprozess von Lifileucel für Kohorten 2, 3 & 4

While Sarnaik et al. [38] documented findings solely from cohort 2, we included more recent and comprehensive data from Chesney et al. [47] in this assessment, encompassing both cohorts 2 and 4 and presenting a pooled analysis of cohort 2 and 4 . The differences in baseline characteristics between the two cohorts are described below (see Table 4-1).

Publikation zu Kohorte 2 & 4 für Assessment herangezogen

4.1.1 Study population

The classification of patients in the Chesney et al. study [47] follows the 7th edition of the tumour-node-metastasis (TNM) classification [48].

Inclusion criteria:

Einschlusskriterien:

- Age ≥18 years
- Unresectable or metastatic melanoma (stage IIIC or stage IV)
- Documented radiologic disease progression
- Progressed following ≥1 prior therapy, including a programmed cell death protein 1 (PD-1)-blocking antibody
- Patients with BRAF V600 mutation-positive melanoma must have progressed on a BRAF or BRAF/MEK (mitogen-activated protein kinase) inhibitor
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Estimated life expectancy of ≥3 months
- Adequate haematologic parameters and organ function
- At least one resectable lesion ≥1.5cm to generate lifileucel
- At least one remaining measurable target lesion

... Pat. ≥18 J., inoperables oder met. Melanom (Stadium IIIC oder IV)

... Fortschreiten nach ≥1 vorheriger systemischer Therapie (inkl. PD1-blockierender Antikörper)

... ≥1 operable Läsion (reseziertes Tumorgewebe von ≥1,5 cm² Durchmesser) zur Herstellung von Lifileucel

Exclusion criteria:

- Organ allograft or prior cell transfer therapy
- Uveal/ocular melanoma
- Hypersensitivity to lifileucel or other study drugs
- Symptomatic and/or untreated brain metastases
- Patients on chronic systemic steroid therapy
- Active systemic infections
- Administration of live or attenuated vaccine within 28 days of non-myeloablative lymphodepletion
- Chronic heart or lung abnormality
- Forced expiratory volume in 1s of ≤60% of the predicted value

Ausschlusskriterien:

... Organtransplantat oder vorherige Zelltherapie

... Uvea-/Augenmelanom

... Überempfindlichkeit gegen Lifileucel

... Pat. unter chron. system. Steroidbehandlung

Table 4-1 presents the main characteristics of the study.

Table 4-1: Characteristics of the included study

Reference/ID	C-144-01 [47]
Study type and design	Phase 2, multicohort, multicentre, open-label study
Study population	Patients ≥18 years of age with unresectable or metastatic melanoma (stage IIIC or stage IV)
Study arms	■ Lifileucel cohort 2 (n=66) ■ Lifileucel cohort 4 (n=87) ■ Cohort 2+4 (n=153)
Study duration, data cut-off and locations	■ Median study follow-up: 27.6 months ■ Data cut-off: 15 September 2021 ■ Multiple trial centres in the USA and Europe
Study endpoints	■ Primary endpoint: ORR ■ Key secondary outcomes: DOR, OS, PFS
Available documentation	■ CSR: not provided ■ Registry entry: NCT02360579 ■ Sponsoring status: sponsored

Abbreviations: CSR ... clinical study report, DOR ... duration of response, n ... number of patients, ORR ... objective response rate, OS ... overall survival, PFS ... progression-free survival

4.1.2 Baseline characteristics

The baseline characteristics of the patients included in the study by Chesney et al. [47] are briefly described in Table 4-2. The complete set of patients' baseline characteristics is available in Chapter 4 in the Appendix. Chesney et al. identified some notable differences in the baseline characteristics between cohort 4 and cohort 2, including a higher proportion of patients with more than three lesions, elevated lactate dehydrogenase (LDH), and liver and/or brain metastases. Additionally, patients in cohort 4 received nearly twice the cumulative duration of prior anti-PD-1/programmed death-ligand 1(PD-L1) therapy. Of note, it was not disclosed if patients were allowed on lower doses of systemic steroid therapy.

Baseline-Charakteristika & Unterschiede in den Kohorten: z. B. mehr Pat. mit mehr als 3 Läsionen in Kohorte 4

Table 4-2: Baseline demographics of participants in the Chesney et al. study [47]

Characteristic	C-144-01 Trial		
Parameter	Lifileucel cohort 2 (n=66)	Lifileucel cohort 4 (n=87)	Lifileucel cohort 2+4 (n=153)
Median age, years (range)	55.0 (20-79)	58.0 (25-74)	56.0 (20-79)
Sex, n (%)			
Male	39 (59.1)	44 (50.6)	83 (54.2)
Female	27 (40.9)	43 (49.4)	70 (45.8)
Screening ECOG performance status, n (%)			
0	42 (63.6)	62 (71.3)	104 (68.0)
1	24 (36.4)	25 (28.7)	49 (32.0)
BRAF V600-mutated, n (%)	17 (25.8)	24 (27.6)	41 (26.8)
Melanoma stage at study entry, n (%)			
IIIC	9 (13.6)	1 (1.1)	10 (6.5)
IV	57 (86.4)	86 (98.9)	143 (93.5)
LDH, n (%)			
≤ULN	39 (59.1)	31 (35.6)	70 (45.8)
1-2×ULN	19 (28.8)	35 (40.2)	54 (35.3)
2×ULN	8 (12.1)	21 (24.1)	29 (19.0)
Median number of therapies (range)	3.0 (1-9)	3.0 (1-8)	3.0 (1-9)
Anti-PD-1/PD-L1, n (%)	66 (100)	87 (100)	153 (100)
Anti-CTLA-4, n (%)	53 (80.3)	72 (82.8)	125 (81.7)
Anti-PD-1 plus anti-CTLA-4 combination, n (%)	34 (51.5)	48 (55.2)	82 (53.6)
BRAF±MEK inhibitor, n (%)	15 (22.7)	24 (27.6)	39 (25.5)
IL-2, n (%)	7 (10.6)	6 (6.9)	13 (8.5)
Primary refractory to anti-PD-1/PD-L1, n (%)	42 (63.6)	41 (47.1)	83 (54.2)
Median cumulative duration of anti-PD-1/PD-L1 therapy before lifileucel (range), months	5.1 (1.4-51.1)	10.0 (0.7-75.8)	7.0 (0.7-75.8)

Abbreviations: CTLA-4 … cytotoxic T-lymphocyte-associated protein 4, ECOG … Eastern Cooperative Oncology Group, IL … interleukin, LDH … lactate dehydrogenase, MEK … mitogen-activated protein kinase kinase, n … number of participants, PD-1 … programmed cell death protein 1, ULN … upper limit of normal

4.1.3 Sample size

The disposition of patients from the Chesney et al. study is detailed in Table 4-3.

Pat.-Verlauf in der Chesney-Studie

Table 4-3: Disposition of patients in the Chesney et al. study [47]

Parameter	C-144-01 Trial
	Lifileucel (pooled cohort 2+4)
Number screened	N/A
Number randomised	189
Number withdrawn/dropout (%)	33 (17.5%)
Number for efficacy analysis (%)	153 (81%)
Number for safety analysis (%)	156 (82%)
Duration of follow-up (median months, range)	27.6 (NR)

Abbreviations: N/A … not available, NR … not reported

4.1.4 Outcomes

In this section, all outcomes defined as critical for evaluating clinical efficacy and safety are marked in **bold**.

Definitions and reporting of critical and important efficacy outcomes

Overall survival is defined as the time from randomisation to death. Survival assessment was conducted every three months via phone to obtain survival status and subsequent anticancer therapy information for up to five years or death, whichever occurred earlier [49].

Gesamtüberleben alle 3 Monate beurteilt

Objective response rate (ORR) is defined as the proportion of patients in a study population who achieve either a partial response (PR) or complete response (CR) as their best overall response (BOR) to treatment. In the Chesney et al. study, the ORR was initially investigator-assessed for cohort 2 but was later switched to being assessed by an independent review committee (IRC). The ORR was defined by Response Evaluation Criteria in Solid Tumors (RECIST) V.1.1 [50].

objektive Ansprechrate von unabhängigem Komitee bewertet

Progression-free survival is defined as the time from randomisation until first evidence of disease progression or death [49].

progressionsfreies Überleben (PFS)

Duration of response is defined as the time from onset of response to progression or death due to any reason, whichever occurs earlier [50].

Ansprechdauer (Ansprechen bis Progression/Tod)

Definitions and reporting of critical and important safety outcomes

In the Chesney et al. study [47], **safety** was assessed by incidence rates, severity, seriousness, relationship to study treatment, and characteristics of treatment-emergent adverse events (TEAEs), which were defined as any adverse event (AE) with onset after lifileucel infusion through day 30 post-infusion. AE and serious AE data were graded as per the Common Terminology Criteria for Adverse Events V.4.03 [47].

Sicherheit mittels Inzidenzraten und behandlungsbedingter unerwünschter Ereignisse bewertet

Study protocol amendments

The primary source of evidence to support efficacy and safety evaluation of lifileucel is from the mentioned phase 2, non-randomised, multicentre, multicohort study (study C-144-01). The study started with a single cohort (cohort 1) and incorporated three additional cohorts. Cohort 2 was introduced in the protocol amendment (Version 5, Feb 4, 2017), while cohort 4 was integrated into another amendment (Version 8, Dec 20, 2018). The hypothesis testing procedure, sample size, and power calculation were only pre-specified for cohort 4.

verschiedene Protokollanpassungen je Kohorte

For the Chesney et al. study, the original primary endpoint for cohort 2 was investigator-assessed ORR. Cohort 4 had a primary endpoint of ORR assessed by an independent review committee. Consequently, the primary endpoint of cohort 2 was amended to IRC-assessed ORR [47].

primärer Endpunkt: objektive Ansprechrate

4.2 Results on effectiveness and safety

The evidence for the effectiveness and safety of lifileucel for treating unresectable or metastatic melanoma is derived from the above-described open-label clinical phase 2 trial [47]. Data were analysed separately for each cohort and as a pooled analysis of the two cohorts (cohorts 2 and 4) to allow for subgroup analyses.

Evidenzbasis bestehend aus einer klinischen Phase-2 Studie: Kohorte 2 & 4 für Evidenzanalyse herangezogen

4.2.1 Clinical efficacy outcomes

Overall survival

Regarding the critical outcome overall survival (OS) (a secondary outcome of the included study), the median OS was 13.9 months (95% confidence interval, CI: 10.6–17.8) and the 12-month OS rate was 54.0% (95% CI: 45.6%–61.6%) in the pooled cohorts (see Table 4-4). The results for OS for separate cohorts are not available.

gepoolte Analyse: medianes Gesamtüberleben bei 13,9 Monaten

Objective response rate

The critical outcome and primary outcome of the study, ORR as assessed by IRC, was 31.4% (95% CI: 24.1%–39.4%) in pooled cohort 2 and cohort 4, with eight complete responses and 40 partial responses. Specifically, ORR for cohort 2 was 34.8% (95% CI: 23.5%-47.6%), and 28.7% (95% CI: 19.5%–39.4%) for cohort 4, see Table 4-4.

objektive Ansprechrate bei 31,4 % (gepoolte Kohorten)

Progression-free survival

Regarding the important outcome PFS (a secondary outcome of the study), the median PFS was 4.1 months (95% CI: 2.8–4.4) and the 12-month PFS rate was 28.3% (95% CI: 20.8%–36.3%) in the pooled cohorts (Table 4-4). The results for PFS for separate cohorts are not available.

gepoolte Analyse: medianes progressionsfreies Überleben bei 4,1 Monaten

Duration of response

Concerning the important outcome DOR (a secondary outcome in the included study), the median DOR was not reached (NR, 95% CI: 8.3 months–NR) at a median study follow-up of 27.6 months in the pooled cohorts. Similarly, it was not reached in cohort 2 (NR, 95% CI: NR–NR); cohort 4: 10.4 months (95% CI: 4.1–NR), meaning the duration was not evaluable since the response was still maintained (see Table 4-4).

gepoolte Analyse: mediane Ansprechdauer bei 27,6 Monaten Follow-up nicht erreicht

Table 4-4: Efficacy results – primary and secondary efficacy endpoints of the Chesney et al. study [47]

Outcome Measure	Lifileucel Cohort 2	Lifileucel Cohort 4	Lifileucel (pooled cohort 2+4)
Study reference/ID	C-144-01 Trial		
Primary outcome			
ORR, n (%), [95% CI]*	23 (34.8), [23.5 – 47.6]	25 (28.7), [19.5 – 39.4]	48 (31.4), [24.1 – 39.4]
BOR, n (%)			
CR	5 (7.6)	3 (3.4)	8 (5.2)

Outcome Measure	Lifileucel Cohort 2	Lifileucel Cohort 4	Lifileucel (pooled cohort 2+4)
Study reference/ID	C-144-01 Trial		
PR	18 (27.3)	22 (25.3)	40 (26.1)
SD	24 (36.4)	47 (54.0)	71 (46.4)
Non-CR/non-PD†	1 (1.5)	0	1 (0.7)
PD	15 (22.7)	12 (13.8)	27 (17.6)
Non-evaluable‡	3 (4.5)	3 (3.4)	6 (3.9)
Secondary outcomes			
DOR median, months (range)§	N/R (1.4+ – 45.0+)¶	10.4 (1.4+ – 26.3+)	N/R (1.4+ – 45.0+)
OS, median	-	-	13.9 months (95% CI: 10.6 – 17.8)
12-month OS rate	-	-	54.0% (95% CI: 45.6% – 61.6%)
PFS, median	-	-	4.1 months (95% CI: 2.8 – 4.4)
12-month PFS rate	-	-	28.3% (95% CI: 20.8% – 36.3%)

Abbreviations: BOR … best overall response, CI … confidence interval, CR … complete response, DOR … duration of response, n … number of participants, N/R … not reached, ORR … objective response rate, OS … overall survival, PD … progressive disease, PFS … progression-free survival, PR … partial response, SD … stable disease

Notes:

** Measured by RECIST V.1.1. Objective response refers to patients with the best overall response of CR and PR. 95% CI for ORR was calculated using the Clopper-Pearson exact test.*

† Patient did not have measurable target lesions by IRC and had best overall response of non-CR/non-PD per IRC assessment.

‡ Six patients were non-evaluable for response (five due to early death; one due to new anticancer therapy).

§ Based on responders and using Kaplan-Meier product-limit estimates.

Critical outcomes are marked in bold.

5-J-Analyse der C-144-01-Studie: ORR: 31,4 % DOR: 36,5 Monate medianes OS: 13,9 Monate

Shortly before finalising the HTA and after the completion of the literature search and study selection for this HTA, a 5-year analysis of the C-144-01 study was presented at the annual American Society of Clinical Oncology (ASCO) meeting 2025 and subsequently published in the *Journal of Clinical Oncology* on 2 June 2025 (Medina et al. [51]). The long-term analysis of cohorts 2 and 4 showed that, of the 153 patients receiving lifileucel, 28 completed five years of follow-up (with the final 5-year cut-off date being 20 November 2024), and the median OS follow-up was 57.8 months. At the data cut-off, lifileucel demonstrated an ORR of 31.4% (48/153 patients; CR 5.9% [9/153], PR 25.5% [39/153]), with 79.3% (111/140) of patients achieving tumour burden reductions. The median time to response was 1.4 months (range 1.3–4.2), and the median DOR was 36.5 months (95% CI: 8.3 to not reached), with some responses ongoing up to 58.7 months. Median OS (OS) was 13.9 months (95% CI: 10.6–17.8), and the 5-year OS rate was 19.7%.

4.2.2 Safety outcomes

Adverse Events (AEs) and serious adverse events (SAEs)

All patients in the safety analysis set (n=156, pooled population of cohort 2 and cohort 4) experienced at least one TEAE of any grade. Grade 3 or 4 TEAEs occurring in ≥30% of the patients included thrombocytopenia (76.9%), anaemia (50.0%), and febrile neutropenia (41.7%). Lymphopenia, observed in 24.4% of patients is an expected outcome of lymphodepleting chemotherapy. The TEAEs were similar between the cohorts, see Table 4-5.

behandlungsbedingte unerwünschte Ereignisse (Grad 3+4) bei ≥30 % der Pat.

Deaths

Six deaths occurred within 30 days after infusion, four of which were attributed to TEAEs (grade 5) and two to progressive disease. From these four TEAEs, three were not related to lifileucel, but to nonmyeloablative lymphodepletion and/or IL-2 (pneumonia, arrhythmia, acute respiratory failure) and one was related to all components of the regimen (intra-abdominal haemorrhage).

6 Todesfälle:
4/6 behandlungsbedingt;
3/4 aufgrund der IL-2-Therapie;
1/4 aufgrund von allen Behandlungen

Table 4-5: Safety results of the Chesney et al. study [47]

Adverse Event	Lifileucel (pooled cohort 2+4) (n = 156)	
Study reference/ID	C-144-01 Trial n (%)	
Preferred term	Any grade, n (%)	Grade 3/4, n (%)
Thrombocytopenia	129 (82.7)	120 (76.9)
Chills	117 (75.0)	8 (5.1)
Anaemia	97 (62.2)	78 (50.0)
Fever	81 (51.9)	17 (10.9)
Neutropenia†	66 (42.3)	45 (28.8)
Febrile neutropenia	65 (41.7)	65 (41.7)
Hypophosphatemia	58 (37.2)	41 (26.3)
Leukopenia†	54 (34.6)	42 (26.9)
Hypotension	52 (33.3)	17 (10.9)
Fatigue	51 (32.7)	6 (3.8)
Lymphopenia†	49 (31.4)	38 (24.4)
Diarrhoea	48 (30.8)	2 (1.3)

Abbreviation: n … number of participants

Note:

† All patients had grade 4 laboratory abnormality per the Common Terminology Criteria for Adverse Events V.4.03 for leukopenia, neutropenia, and lymphopenia during the treatment-emergent period. Only clinically significant laboratory abnormalities as per investigators were reported as adverse events.

The above-mentioned 5-year analysis of cohorts 2 and 4 published by Medina et al. [51] showed that among 156 patients in the safety population, 12 (7.7%) died due to AEs of any cause; four deaths (2.6%) occurred within 30 days, and eight deaths (5.1%) occurred after 30 days post-infusion. Treatment-related deaths occurred in five patients (3.2%), primarily within 30 days and attributed to pneumonia, arrhythmia, acute respiratory failure, intra-abdominal haemorrhage, and bone marrow failure. All patients experienced grade 3/4 haematologic abnormalities following non-myeloablative lymphodepletion (NMA-LD), including lymphopenia by day 5, with most cytopenia resolving to grade ≤2 by day 30; platelet and red blood cell transfusions were mainly needed within the first 14 days after lymphodepletion initiation. AEs were consistent with the known safety profiles of NMA-LD and interleukin-2 (IL-2), and rapidly decreased within two weeks after lifileucel infusion, with no new or late-onset AEs related to lifileucel.

5-Jahres-Analyse der C-144-01-Studie:
5 Todesfälle durch die Therapien (3,2 %)

Alle Pat. hatten Grad 3/4 hämatologische Anomalien

4.2.3 ESMO-MCBS scorecard for lifileucel

According to the European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS), lifileucel was rated with a score 2, indicating that it has no substantial clinical benefit. (see Table 4-6) [44]

kein bedeutsamer klin. Zusatznutzen von Lifileucel gemäß der ESMO-MCBS (Score 2/5)

Table 4-6: ESMO-MCBS of lifileucel [52]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	3	NA	ORR: 31.4% (CI 95%: 24.1–39.4)	NA	ORR (PR+CR) ≥20–<60% AND DOR ≥9 months	3	41.7% febrile neutropenia grade 3–4	NA	-1	2

Abbreviations: AJ … adjustment, CI … confidence interval, CR … complete response, DOR … duration of response, ESMO-MCBS … European Society for Medical Oncology-Magnitude of Clinical Benefit Scale, FM … final magnitude of clinical benefit grade, HR … hazard ratio, Int … intention, MG … median gain, NA … not available, NC … non curative, ORR … objective response rate, PM … preliminary grade, PR … partial response, QoL … quality of life, ST … standard treatment

4.3 Quality of evidence

Risk of Bias

For the Chesney et al. study [47], several risks of bias were identified. The study had an open-label design without a comparator. Additionally, an IRC measured the primary endpoint objectively; however, for cohort 2, the primary endpoint was initially investigator-assessed and then was changed to IRC-assessed. It is also unclear how appropriate it is to pool cohorts 2 and 4 retrospectively, as it was not pre-specified in the study protocol (see above for several study protocol amendments). The authors report that some notable differences were observed in the baseline characteristics between cohorts 2 and 4. Overall, it was concluded that the study was of moderate methodological quality.

Risk of Bias (RoB; Verzerrungsrisiko)

u. a. unterschiedliche Krankheitsstadien bei Studieneintritt; Änderung der Endpunktbewertung

Statistical analysis and inconsistencies

kein statistischer Analyseplan verfügbar

No statistical analysis plan was available for the Chesney et al. study [47] and the pooling of cohorts 2 and 4 was not pre-specified. The study started with cohort 1, and cohort 2 was added in a later protocol amendment without any formal hypothesis testing plan. Only cohort 4 had a prespecified hypothesis testing procedure on the primary endpoint. Therefore, the primary efficacy analysis was conducted solely on the data from cohort 4. Pooled data from cohort 2 and cohort 4 were later used as supportive evidence for efficacy. The statistical analysis is detailed in Chapter 4 in the Appendix.

External validity and applicability

Übertragbarkeit der Studienergebnisse auf klinische Praxis limitiert

The applicability of evidence from the Chesney et al. study [47] of lifileucel in stage III and stage IV melanoma for the Austrian context faces significant barriers. This is due to the requirement for specialised cell therapy infrastructure, centralised good manufacturing practice facilities, expertise in TIL cell production and systems for managing the complex treatment protocol and associated toxicities. The generalisability to populations other than immunotherapy-resistant patients with limited therapeutic options may be uncertain, and the study's restriction against bridging therapy between tumour resection and lifileucel infusion may not reflect real-world clinical practice where such therapies might be necessary for rapidly progressing patients. Additionally, the absence of direct comparators prevents a full contextualisation of the clinical value of lifileucel relative to other available options. While the study demonstrated efficacy in OS and DOR, no information on quality of life is available. See details in Chapter 4 in the Appendix.

Certainty of evidence according to GRADE

Vertrauenswürdigkeit der Evidenz nach GRADE

The ranking according to the grading of recommendations assessment, development and evaluation (GRADE) scheme can be found in the summary of findings tables below (Table 4-7) and the evidence profile in Chapter 4 in the Appendix.

niedrige bis sehr niedrige Vertrauenswürdigkeit (einarmige Studie)

Overall, the certainty of evidence for the effectiveness and safety of the one included single-arm study [47] for lifileucel was graded as low to very low.

Table 4-7: Summary of findings table for the Chesney et al. study [47]

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)[2]
Efficacy			
ORR	ORR, n (%) 48 (31.4; 95% CI, 24.1–39.4)	153	⊕⊕◯◯ low
DOR	DOR median, months (range), N/R (1.4+ – 45.0+)	153	⊕⊕◯◯ low
OS	OS, median, 13.9 months (95% CI: 10.6–17.8)	153	⊕◯◯◯ very low
PFS	PFS, median, 4.1 months (95% CI: 2.8–4.4)	153	⊕◯◯◯ very low
QoL	Not reported	-	-

[2] As an uncontrolled trial, this study begins with low-certainty evidence due to the lack of randomisation and control group. Further downgrading occured due to the moderate methodological quality comprising change of the primary endpoint measurement, appropriateness of cohorts pooling and missing long-term data. ORR and DOR were upgraded due to efficacy results.

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)[2]
Safety			
Grade 3/4 adverse events	■ Thrombocytopenia (76.9%) ■ Anaemia (50.0%) ■ Febrile neutropenia (41.7%) ■ Deaths, n=6	156	⨁◯◯◯ very low

Abbreviations: CI...confidence interval, DOR...duration of response, GRADE...grading of recommendations assessment, development and evaluation, n...number, N/R...not reached, QoL ... quality of life, ORR...objective response rate, OS...overall survival, PFS...progression-free survival

5 Price comparisons, treatment costs and budget impact

The Austrian National Public Health Institute (Gesundheit Österreich GmbH, GÖG) found no official price information for lifileucel in 16 surveyed countries (14 EU member states, Norway and the United Kingdom (UK)), as lifileucel is not approved by the European Commission (EC) yet.

keine offiziellen Preisinfos zu Lifileucel für Europa vorhanden

For Austria, the pharmaceutical company reported a US list price for lifileucel of $562,000 [54], which they converted to €506,000 and used as a placeholder price in this report.

Angaben des Unternehmens: US-amerikanischer Preis von $ 562.000 (€ 506.000)

5.1 Pharmacoeconomic model(s)

5.1.1 Economic evaluation based on pharmaco-economic models

We could not identify any international pharmacoeconomic evaluation or HTA report with a pharmacoeconomic evaluation for lifileucel through the systematic literature search or additional manual searches. However, we identified studies that examined the cost-effectiveness (CE) of tumour-infiltrating lymphocytes (TIL; *in-house products of Dutch hospitals*), which we describe in more detail in the summary below.

keine publizierten gesundheitsökonomische n Evaluationen zu Lifileucel identifiziert, jedoch zu „in-house" Produkten

Summary of existing economic evaluations of academic TIL products

Characteristics of the economic evaluations and applied models

We identified two health economic evaluations that examined the CE of hospital in-house produced products, *tumour-infiltrating lymphocytes* (TIL), compared to ipilimumab in second-line or later treatment for advanced melanoma. Both studies assumed that a non-profit hospital undertakes the production of the TIL infusion. Moreover, the costs of the TIL treatment, including tumour resection, TIL isolation, production, hospital admission, and follow-up, were collected at a patient level by each treatment centre. The main characteristics of the studies are described below and in more detail in Chapter 5 in the Appendix.

2 gesundheitsökonomische Evaluationen zu TIL-Produkten, die in Krankenhäusern produziert werden

The first identified study used the Dutch healthcare perspective, and it was conducted as a part of Coverage with Evidence Development (CED) programme led by the Netherlands Cancer Institute (NKI) [55]. It estimated the early CE of TIL using model-based simulation of a cohort of 1,000 patients with metastatic melanoma (stage IV) and starting age of 52. The second identified study followed a modified societal perspective, accounting also for non-healthcare-related costs, which comprised out-of-pocket expenses, homecare costs, productivity losses of patients and productivity losses and treatment-related travel costs of family and friends [56]. It was based on a multicentre, open-label randomised phase-3 clinical trial [57] conducted at NKI and Danish National Center for Cancer Immune Therapy (CCIT-DK). The Dutch (NL) system represented the base case, while the Danish (DK) setting was explored in a scenario analysis.

zwei Studien (2018/2024):
1 Gesundheitssystem-Perspektive &
1 gesellschaftliche Perspektive,
Markov-Modell mit
3 Gesundheitszuständen,
Pat.-spezifische Unterschiede bei metastasiertem Melanom,
gemeinnützige Produktion

Both studies used a similar Markov model with three mutually exclusive health states: stable disease/progression-free survival (PFS), progressed disease (PD) and death (all causes). Results were illustrated using a CE plane and cost-effectiveness acceptability curves (CEACs).

niederländischer WTP-Schwellenwert:
€ 80.000 pro QALY;

Moreover, both studies applied a Dutch willingness-to-pay (WTP) threshold of €80,000 per incremental quality-adjusted life-year (QALY) [55, 56]. For the DK scenario analysis in one study, an informal WTP-threshold of €50,000 per incremental QALY was applied [56].

Ten Ham mit zusätzlichem dänischem Szenario
(€ 50.000 pro QALY)

The uncertainty in the input parameters was addressed probabilistically using Monte Carlo simulation (10,000 iterations) with assigned distributions for parameters in both studies [55, 56]. One-way sensitivity analyses were also conducted, varying parameters by ±25% in Retel et al., 2018 [55] and varying input values one by one between pre-set minimum and maximum values, which were informed by 95% confidence intervals (CIs) or variance of the mean by ±20% in Ten Ham et al., 2024 [56].

Sensitivitätsanalysen:
Monte-Carlo-Simulation gemäß CHEERS-Richtlinien

Results of the health economic evaluations

Both model-based economic evaluations demonstrated that TIL therapy produced in academic non-profit hospitals is cost-effective compared to ipilimumab for advanced melanoma treatment [55, 56].

With the TIL production cost of €35,000, the early model-based evaluation found that TIL generated more QALYs (0.45 vs 0.38) at lower costs (€81,140 vs €94,705) than ipilimumab, resulting in a dominant deterministic incremental cost-effectiveness ratio (ICER) (see Table 5-1). This finding proved robust across sensitivity analyses, with TIL remaining cost-effective up to the production costs amounting to €50,500. Probabilistic sensitivity analysis, however, indicated a considerable amount of uncertainty, as 44% of the results of the Monte Carlo simulations were spread over three quadrants in the CE-plane. CEACs showed TIL dominating ipilimumab with an 86% probability of cost-effectiveness at the Dutch €80,000 per QALY gained threshold [55].

Studie 1:
TIL-Therapie aus gemeinnütziger Produktion kosteneffektiv (bei Produktionskosten bis zu € 50.500) vs. IPI bei fortgeschrittenem Melanom

The subsequent trial-based analysis confirmed these findings with more robust data. TIL maintained higher effectiveness (3.52 vs 2.46 undiscounted QALYs) and lower lifetime societal costs (€347,168 vs €433,634 in NL; €337,309 vs €436,135 in DK), with production costs of €67,547. Probabilistic sensitivity analysis showed TIL maintained >99% probability of cost-effectiveness at respective national thresholds (€80,000 in NL, €50,000 in DK). The results remained consistent across 5-year, 10-year, and lifetime horizons [56].

Studie 2:
TIL zeigte niedrigere Kosten von einer gesellschaftlichen Perspektive für NL & DK bei TIL-Produktionskosten von € 67.547

Table 5-1: Overview of results of CE studies of TIL

Author, year [reference]	Country	Incremental costs (base-case: TIL vs IPI)	Incremental effects (base-case: TIL vs IPI)	ICER (base-case)
Retèl 2018 [55]	NL	€81,140 vs €94,705	LYs: 0.70 (8.4 months) vs 0.58 (7 months) QALYs: 0.45 vs 0.38	Dominant ICER (TIL more effective and less costly)
Ten Ham, 2024 [56]	NL and DK	NL base case, undiscounted, lifetime horizon: €347,168 vs €433,634 DK scenario: €337,309 vs €436,135	Lifetime horizon (undiscounted): LYs: 4.47 vs 3.33 QALYs: 3.52 vs 2.46	Dominant ICER

Abbreviations: CE … cost-effectiveness, DK … Denmark, ICER … incremental cost-effectiveness ratio, IPI … ipilimumab, LY … life-years; pts: patients, NL … Netherlands, QALYs … quality-adjusted life-years, TIL … tumour-infiltrating lymphocyte

The limitations of the reported results stem from the fact that TIL therapy studied in these analyses was directly produced by academic hospitals/research institutes, and consequently, presented lower treatment costs compared to commercially sourced TIL. In addition, the standard of care in this indication has since moved from ipilimumab monotherapy to ipilimumab plus nivolumab. However, as the price of ipilimumab/nivolumab is substantial, authors hypothesised that a significant difference in survival would be necessary to change the conclusion of their study [56].

Nonprofit-Produktion niedrigere Kosten als kommerzielle TIL; veralteter Vergleich mit IPI-Monotherapie statt aktuellem NIVO plus IPI-Standard

In addition, we identified a study that evaluated the cost-effectiveness of likely TIL-adoption scenarios [58]. The cost-effectiveness model previously described by Retel et al. (2018) [55] served as the base case model for accommodating selected adoption scenarios developed using a Delphi approach involving experts. One evaluated scenario included "TIL production outsourced" to a commercial producer. Since no commercial price of TIL was available, the authors assumed that the commercial price of TIL would be at least three times higher than the academic production cost, resulting in a deterministic value of €106,500. This modification in production costs resulted in an overall cost of €152,085 for TIL therapy. Ipilimumab costs were held constant at €94,705.

kommerzielles TIL-Szenario mit mindestens dreifach höheren Produktionskosten (€ 106.500 pro Anwendung) führt zu Gesamtkosten von € 152.085 vs. € 94.705 für Ipilimumab

The results of the scenarios incorporated into the CE-model were expressed as the ICER, net monetary benefit (NMB), and the probability of TIL therapy being cost-effective. With all other parameters unchanged, the scenario of "TIL production outsourced" resulted in an ICER of €1,138,642 per QALY gained, with TIL being dominated by ipilimumab. Moreover, at the Dutch WTP-threshold of €80,000 per QALY gained, this scenario showed a negative NMB of -€51,551 and 0% likelihood of becoming cost-effective compared to ipilimumab. The "TIL production outsourced" scenario showed a positive, albeit limited, 11% likelihood of being cost-effective only when combined with two additional scenarios: "TIL more effective" (assumed 10% increase of PFS and OS rates) and "automatic TIL production" (30% decrease of production costs).

ICER von € 1.138.642/QALY, negative NMB (–€ 51.551), 0 % Kosteneffektivität bei € 80.000-Schwellenwert; nur mit besserer Wirksamkeit (+10 % PFS/OS) & automatisierter Produktion (–30 % Kosten)

5.3 Budget impact analysis

5.3.1 Self-calculated budget impact analysis for the Austrian context before negotiation

Eligible population and market share in years 1–3

primäre Analyse: erwartete Pat. für Lifileucel: 17 pro Jahr

According to our clinician-validated estimate, there would be around 17 patients per year eligible for lifileucel treatment in Austria, summing up to 51 patients over the three-year horizon. This number is assumed to remain constant over the next three years in the primary analysis, as we do not expect rises in the incidence.

hergeleitet durch Melanom-Inzidenz → 186 fortgeschrittene Fälle → 87 theoretisch geeignet → 20 % praktisch behandelbar aufgrund Präselektionskriterien und Zentrumskapazitäten

In deriving the target population, we used annual melanoma incidence data for Austria, foreign data on distribution of cancer stages and sub-stages [19] and clinical expert estimation. Overall, we estimate that there are 186 newly diagnosed cases per year with unresectable or advanced melanoma who shall undergo the first-line standard of care (SoC) treatment with the PD-L1 inhibitor (i.e. nivolumab; either in monotherapy or in combination with CTLA-4 blocking antibody ipilimumab). Long-term follow-up data on first-line treatment with nivolumab shows that approximately 60% of treated patients need subsequent therapy [59]. Estimated 55% of melanoma patients constitute BRAF wild-type and, based on the indication, would be eligible for lifileucel treatment at this stage (n=62). The subpopulation harbouring BRAF V600 mutation (around 45%) [24] could be additionally treated with BRAF/MEK inhibitor combination, and approximately half of these patients need subsequent therapy (n=25) [60]. Altogether, 87 patients would be eligible for lifileucel treatment according to the proposed indication each year, adding up to 261 patients in three years. However, considering the preselection criteria suggested for the identification of the patients who will most likely benefit from lifileucel treatment, as well as the organisational capacities in Austrian centres authorised for the administration of cell therapies, we further restrict this population to 20% in the first three years following launch (based on Austrian clinical expert estimations). These patients are the expected candidates for lifileucel treatment in the primary scenario of this analysis. The derivation of the population is displayed in more detail in Chapter 5 in the Appendix.

Treatment costs of lifileucel per patient and gross budget impact years 1–3

Anschaffungskosten Lifileucel-Einmalinfusion pro Pat.: € 506.000, für 17 Pat.: € 8,6 Mio. pro Jahr & € 25,8 Mio. für 3 Jahre

Currently, no price is available for lifileucel in Europe. The manufacturer submitted the proposed list price for Europe of €506,000, based on the lifileucel wholesaler price of $562,000, using the currency exchange ratio as of 3 April 2025 [54] and representing the cost for one-time infusion of lifileucel per patient[3]. For the estimated patient population of 17 patients annually, the total drug acquisition cost would be approximately €8.6 million annually, resulting in around €25.8 million over the next three years (see Table 5-2).

[3] The marketing authorisation holder (MAH) did not specify if other cost categories than the lifileucel acquisition costs are included in the price.

Additional treatment costs

In addition to the lifileucel infusion, the lifileucel treatment comprises surgery for tumour tissue procurement, non-myeloablative lymphodepletion, administration of high-dose IL-2 and the treatment of adverse events (i.e. strongly recommended use of filgrastim), resulting in an overall 21-day hospital stay [35]. According to [58], 10% of the patients need a stay in the intensive care unit after lifileucel infusion. According to the Austrian clinical experts, this can be much higher. This uncertainty in the costs of the inpatient stay needs to be considered. We added all additional costs to the lifileucel acquisition cost to obtain the direct medical cost of lifileucel treatment of €560,903 per patient. For the estimated patient population of 17 patients annually, the total direct medical cost of treatment is projected to be approximately €9.1 million annually, resulting in around €27.3 million over a three-year period. Lifileucel acquisition costs constitute the largest proportion of these expenses (94.5%, see Table 5-2).

gesamte direkte Kosten von Lifileucel einschließlich Begleittherapien:
€ 560.903/Pat.
→ bei 17 Pat./Jahr:
€ 9,1 Mio. jährlich bzw.
€ 27,3 Mio. über 3 Jahre

Table 5-2: Cost of lifileucel scenario including additional treatment costs

Cost categories	per patient	Year 1	Year 2	Year 3	Total	%
Drug acquisition	€506,000	€8,602,000	€8,602,000	€8,602,000	€25,806,000	94.5
Drug administration (tumour tissue resection, hospitalisation)*	€47,956	€385,310	€385,310	€385,310	€1,155,931	4.2
Pretreatment (non-myeloablative lymphodepletion)	€2,021	€34,357	€34,357	€34,357	€103,071	0.4
Post-treatment (IL-2 and AE management)	€4,926	€83,734	€83,734	€83,734	€251,201	0.9
Sum: Total direct medical costs of lifileucel including additional treatment costs	€560,903	€9,105,401	€9,105,401	€9,105,401	€27,316,203	100

Abbreviations: AE … adverse event, IL-2 … Interleukin-2

*Note: *According to [58], 10% of the patients need a stay in the intensive care unit after lifileucel infusion. According to the Austrian clinical experts, this can be much higher. This uncertainty in the costs of the inpatient stay needs to be considered.*

Standard of care costs

The SoC in the proposed indication consists of PD-1-based immunotherapy (nivolumab, NIVO) in combination with either CTLA-4 blocking antibody (ipilimumab, IPI) or LAG3-antibody (relatlimab). According to clinical experts, most patients (80%) in Austria receive treatment with NIVO+IPI, while the remainder (20%) receive treatment with NIVO + anti-LAG3. In contrast to lifileucel therapy, treatment with SoC agents does not routinely require pretreatment and post-treatment supportive therapies and does not require hospitalisation as it can be administered in the ambulatory setting; hence, direct medical costs associated with SoC treatments equal the acquisition costs. Additionally, the median treatment duration for SoC, in terms of number of cycles, was based on Austrian expert estimates for this pre-treated population to approximate clinical practice (four 3-week cycles for NIVO+IPI, three 4-week cycles for NIVO+anti-LAG3).

SoC:
80 % NIVO + IPI,
20 % NIVO + anti-LAG3
in Ö
keine Begleittherapie standardmäßig nötig
→ Behandlungsdauer nach Expert:innen-Angaben für vorbehandelte Population

Per-patient costs of SoC treatment in the SoC-scenario without lifileucel are €89,576 for NIVO+IPI (four 3-week cycles) and €34,590 for NIVO+anti-LAG3 (three 4-week cycles)[4]. In the estimated population of 87 patients, the treatment cost with SoC amounts to approximately €6.8 million per year and €20.4 million over a three-year period. Detailed calculations are presented in Table 5-3.

gesamte direkte Kosten im SoC-Szenario:
€ 124.166/Pat.
→ bei 87 Pat./Jahr:
€ 6,8 Mio. jährlich bzw.
€ 20,4 Mio. über 3 Jahre

Table 5-3: Cost of SoC scenario without lifileucel

SoC	per patient	n pts (%)	Year 1	Year 2	Year 3	Total
NIVO+IPI	€89,576	69 (80)	€6,180,744	€6,180,744	€6,180,744	€18,542,232
NIVO+ relatlimab	€34,590	18 (20)	€622,620	€622,620	€622,620	€1,867,860
Sum: Total direct medical costs of SoC scenario WITHOUT lifileucel			€6,803,364	€6,803,364	€6,803,364	€20,410,092

Abbreviations: IPI … ipilimumab, NIVO … nivolumab, n … number, pts … patients, SoC … standard of care

For the lifileucel scenario, we assumed that patients who progress after anti-PD-L1 and, in case of BRAF+, after BRAF inhibitor with or without MEK-inhibitor, but who would not be suitable candidates for lifileucel therapy (n=70 per year, 210 over 3 years), will be treated with the current SoC in the indicated proportion. The total direct medical costs associated with SoC treatment of these patients are €5.5 million per year and €16.5 million over three years, summing up to total direct medical costs of the lifileucel scenario of €14.6 million annually and €43.8 million over three years. Details of the overall cost of treating the population non-eligible for lifileucel are also presented in Table 5-4.

SoC-Kosten im Lifileucel-Szenario:
bei 70 Pat./Jahr:
€ 5,5 Mio. jährlich bzw.
€ 16,5 Mio. für 3 Jahre

Gesamtkosten Lifileucel-Szenario:
€ 14.6 Mio./Jahr bzw.
€ 43,8 Mio. für 3 Jahre

[4] The number of considered cycles reflects the mean number of cycles reported in clinical studies and by Austrian clinical experts.

Table 5-4: Cost of the lifileucel scenario including SoC costs

SoC+lifileucel	Per patient	N pts (%)	Year 1	Year 2	Year 3	Total
Lifileucel	€560,903	17 (20)	€9,105,401	€9,105,401	€9,105,401	€27,316,203
SoC: NIVO+IPI	€89,576	56 (64)	€5,016,256	€5,016,256	€5,016,256	€15,048,768
SoC: NIVO+ relatlimab	€34,590	14 (16)	€479,876	€479,876	€ 479,876	€1,439,628
Sum: Total direct medical costs of scenario with lifileucel			€14,601,533	€14,601,533	€14,601,533	€43,804,599

Abbreviations: IPI ... ipilimumab, NIVO ... nivolumab, n ... number, pts ... patients, SoC ... standard of care

Net drug-budget impact in years 1–3

The estimated net budget impact of reimbursing lifileucel therapy for 17 patients per year is around €23.4 million over a three-year period. Assuming that before the lifileucel introduction, 80% of these patients would be treated with IPI+NIVO and 20% with NIVO + relatlimab, the savings on the SoC represent around €1.3 million per year and €3.9 million over three years. By contrast, treating these patients with lifileucel will cost around €9.1 million per year and €27.3 million over three years.

€ 3,9 Mio. Einsparungen bei Standardtherapie innerhalb von 3 Jahren durch Einführung von Lifileucel, jedoch zusätzliche Kosten von € 27,3 Mio.

Comparison of lifileucel scenario vs current SoC scenario in Austria

As reported above, the total direct medical costs of the lifileucel scenario are projected to be approximately €14.6 million annually assuming 17 eligible patients per year, finally summing up to €43.8 million over three years. Costs associated with the acquisition of lifileucel and its additional treatment requirements account for 62.4% of the total expenditure, while the other 37.6% of the costs refer to the SoC costs for the patients possibly ineligible for lifileucel. In contrast, if lifileucel is not introduced, and patients continue receiving SoC as usual, only around half of the costs (€20.4 million for three years) would be needed Figure 5-1.

Lifileucel-Szenario der indizierten Population rund doppelt so teurer als das Standardtherapie-Szenario über die nächsten 3 Jahre

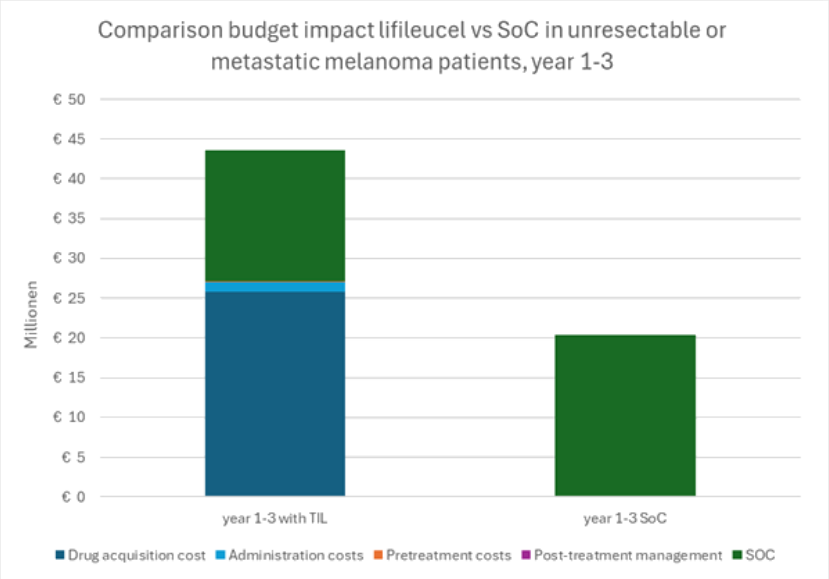


Figure 5-1: Comparison of total direct medical costs of lifileucel scenario vs current SoC scenario for 3 years (primary scenario)

Scenario analysis using patient number assumptions from the clinical experts and increasing incidence rates over the years

Szenario-Analyse: steigende Pat.-Anzahl für Lifileucel (1. Jahr: 10 % – 3 Jahr: 30 %) und steigende Inzidenzrate von 2 %

In this scenario analysis, we applied two further assumptions that can be expected to be observed in a real-world setting. First, we modified the market uptake of lifileucel, assuming gradually increasing market penetration [year 1: n=9 (10%); year 2: n=18 (20%); year 3: n=27 (30%)]. This modification reflects the range of numerical estimates of suitable candidates for lifileucel treatment as a proportion of the overall eligible population provided by the clinical experts. In addition, we hypothesised that there could be a concomitant 2% annual increase in the incidence of unresectable and advanced melanoma, as we found evidence of such a trend in the UK [61]. The result is an increase in the overall eligible population over a three-year period, totaling 265 patients, compared to the 261 patients used in the primary analysis. Consequently, in year three, there would be 90 eligible patients, 30% of whom (n=27) would eventually receive the lifileucel treatment.

Gesamtkosten Lifileucel-Szenario: € 10,4 Mio. in Jahr 1 bis € 19,4 Mio. in Jahr 3 = € 44,5 Mio. für 3 Jahre

Verhältnis gegenüber dem Standardtherapie-Szenario bleibt annähernd gleich

The net budget impact over three years does not differ substantially, amounting to approximately €24.3 million over three years, compared to €23.4 million obtained in the primary analysis. The savings on the SoC in the lifileucel scenario represent around €4.3 million over three-year period. The total direct medical costs of the lifileucel scenario, also including the SoC treatment costs of the patients assumed ineligible for lifileucel, would be €10.8 million in year one, €15.0 million in year two, and €19.4 million in year three, totaling €45.2 million over three years compared to €43.8 million in the primary analysis. If lifileucel is not introduced, and patients continue receiving SoC as usual, the total direct medical costs in the scenario analysis would amount to €20.8 million (see Figure 5-2). Overall, the expenditure on the lifileucel scenario compared to the SoC scenario is approximately double, both in the primary and the scenario analysis.

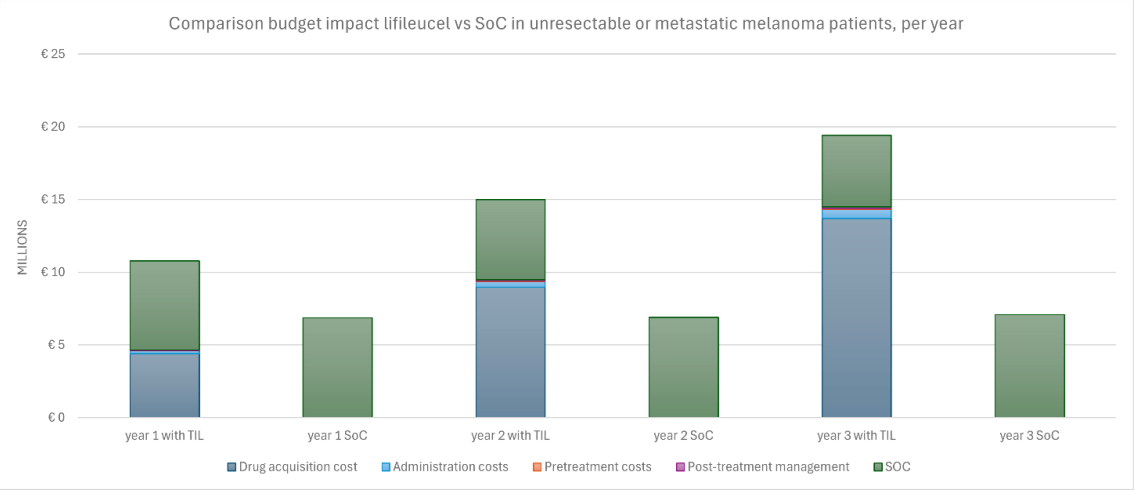


Figure 5-2: Comparison of total direct medical costs of lifelore scenario vs current SoC scenario for 3 years (scenario analysis: annually increasing market penetration rates and incidence rates)

Indirect costs

keine indirekten Kosten berücksichtigt

Standardised and widely accepted data on indirect healthcare costs are unavailable in Austria. Therefore, we followed the healthcare perspective for the analysis and did not consider indirect costs, which constitutes a limitation of the analysis.

6 Extended perspectives

6.1 Stakeholder perspectives

trotz insgesamt verbesserter Prognose schreitet Erkrankung häufig fort

Bedarf an sicheren, wirksamen Zweit- und Drittlinientherapien

Melanoma represents a significant public health challenge due to its increasing incidence and potential for metastasis. Although patient outcomes drastically improved due to progress of targeted drugs and immunotherapy [14], many patients experience disease progression after first- or second-line treatments, and the overall survival (OS) rate at later stages is still low. Therefore, an unmet need exists for novel, safe, and effective therapies for patients with advanced melanoma to improve the standard of care (SoC) in the second-line setting (for patients with BRAF wild-type tumours) and third-line setting (for patients with BRAF V600 mutation-positive tumours) [62]. If licensed, lifileucel will provide an additional treatment option for patients with previously treated unresectable or metastatic melanoma, and for patients who have progressed on multiple therapies [63].

Organisational aspects

TIL-Produktion ist technisch herausfordernd

zeitnahe und effiziente Planung entscheidend

The process of manufacturing tumour-infiltrating lymphocytes (TIL), such as lifileucel, is technically challenging [24], and the administration has the potential to substantially impact healthcare infrastructure, utilisation, and service delivery [62]. Considering the challenges of managing advanced disease and the multiple steps required for TIL therapy, timely and efficient planning and operational execution are critical [35].

Lifileucel: komplexer organisatorischer Prozess

Operational considerations for lifileucel therapy include the streamlining of patient selection algorithms and support (e.g., patient education, timely referral), institutional capacities and infrastructures, surgery, shipping logis-tics (precise scheduling, temperature control), nursing support (training, guidelines), pharmacy support, cell therapy lab capacities, manufacturing and data/electronic medical record management. Chapter 6 of the Appendix overviews the required operational steps [35].

Pat.-Selektion schwierig: multidisziplinäres Team und (zeitliche) Optimierung des Behandlungsweges nötig

Regarding patient selection, case discussion in a multidisciplinary tumour board setting, including a dermato-oncologist, surgeon, medical oncologist, and a physician specialising in cellular therapy is mandatory [35]. Since identifying potential candidates for the therapy can be challenging, streamlining the referral pathway to TIL is crucial. Awareness of this therapeutic option can be enhanced through patient engagement materials, education, and patient advocacy, which can improve understanding of the TIL therapy process and treatment expectations. Increased awareness among physicians could support dermato-oncologists and medical oncologists in determining the best way to integrate TIL into clinical practice and ensure timely referrals [35].

hohe Kosten durch erwarteten Preis von Lifileucel + Schaffung der benötigten Infrastruktur

Medical experts indicated that lifileucel will likely have a significantly high per-patient cost [62]. Since the TIL therapy's manufacturing process is complex and expensive (involving the isolation, expansion, and reinfusion of TILs into patients), costs increase due to the need for specialised facilities, extensive labour demands associated with rising need for qualified personnel, and stringent quality control measures. Additionally, the personalised nature of TIL therapy means that each batch is patient-specific, which further drives up costs. Collaborations between academic institutions, industry, and regulatory bodies could help innovate TIL therapy and share the burden of high initial

costs. Continued research and clinical trials are required to refine TIL therapy protocols, improve effectiveness, and reduce costs. Identifying those patients who are most likely to benefit from TIL therapy is essential to ensure that resources are directed toward those who are most likely to derive clinical benefits [64]. However, implementing TIL therapy in advanced melanoma patients might reduce healthcare utilisation associated with subsequent treatments and other disease-related supportive measures [62].

Health delivery process and management

sorgfältige Planung aller Therapieschritte erforderlich

The multiple operational considerations for TIL therapy were described above and can be found in Chapter 6 in the Appendix [35]. The one-time infusion with lifileucel is a complex process requiring hospitalisation (approximately three weeks), specialised and trained personnel, patient monitoring, and well-equipped centres [30]. Reduction of hospitalisation to one to two weeks is possible if tumour surgery and lifileucel administration could be conducted outpatient. However, this does not meet the requirements of the Austrian healthcare system. Careful planning is required for the safe and timely execution of all necessary steps [36]. Since the therapy's administration, along with lymphocyte-depleting therapy and cytokines, poses a high risk for adverse events (AEs) [62], an intensive care facility and specialists skilled in cardiopulmonary or intensive care medicine must be available [26]. Hence, not all hospitals can implement safe delivery of lifileucel [62], which may pose the risk of inequity in patient access to lifileucel [26].

hohes Risiko für unerwünschte Effekte: Intensivstation muss verfügbar sein

Voraussetzungen nicht in allen Spitälern gegeben

klin. Expert:innen: bereits jetzt Ressourcenproblem, suffiziente Infrastruktur für TIL-Therapie erforderlich

According to clinical experts, the improved availability of cell therapies (in particular of CAR T-cell therapy for lymphoma and myeloma) in Austria already leads to a structural and personnel resource problem in the cell therapy centres. This situation would be further aggravated by the approval of lifileucel as this will increase patient numbers to be treated in specialised cell therapy wards. For the safe delivery of TIL therapy, a sufficient infrastructure must be established in advance, and, in addition, a legal framework is required for new therapies in general.

TIL nicht für Pat. mit rasch fortschreitender Erkrankung aufgrund mehrwöchiger Produktionsdauer geeignet

As mentioned earlier, TIL product manufacturing takes several weeks. Thus, TIL therapy may not be the best option for patients with rapidly progressing disease [26, 36]. Hence, improvements must be made regarding how therapies can be manufactured more quickly and delivered timely for patient use in these difficult cases [14].

6.2 Patients' perspective

2 Pat. haben den Fragebögen ausgefüllt

Two patients completed the patient questionnaire. None of them were members of a patient organisation. The characteristics of the participants are described in

Table 6-1.

Table 6-1: Characteristics of participants of the structured patient questionnaires (n=2) conducted by the AIHTA

Patient characteristics	Total number of patients (n=2)
Sex	
Female	2
Male	0
Median age (years)	48
Diagnosis (self-reported)	Malignant melanoma stage IV (n=2)
Role	
Patient	2
Carer	0
Member of a patient organisation	
Yes	0

Abbreviations: AIHTA … Austrian Institute for Health Technology Assessment, n … number of patients

Herausforderung, Pat. für die Befragung zu finden, wahrscheinlich dem Stadium der Erkrankung geschuldet

Due to the lack of a patient organisation in Austria for melanoma patients, finding patients in this stage of the disease who were able and willing to answer the questionnaire was challenging. We then found a private Austrian self-help group for melanoma patients, but only two patients responded to the request for participation and completed the questionnaire. All the more, our thanks go to the two patients who answered our questions with remarkable candour.

Lebensqualität durch Melanom reduziert, lebensverändernde Diagnose einschneidend

Melanoma is known to cause physical and mental health deficits that lead to impairments in patients' health-related quality of life (HRQoL) [65]. Although new treatment options have substantially improved the prognosis in patients with metastatic melanoma, approximately 50% still die from the disease within five years after the diagnosis of stage IV [57]. Considering this, it is obvious that many patients' journeys begin with the unexpected change from being a previously healthy person to one with an invasive disease and a vastly shortened life expectancy [65]. One patient answering the AIHTA survey reported that she felt "broken" by the cancer diagnosis and lost her faith in the good [66].

häufige physische Symptome bzw. Nebenwirkungen von Therapien: Fatigue, Kopfschmerzen, Schmerzen in Gliedmaßen, Durchfälle, Konzentrationsprobleme etc.

By the time patients reach an advanced stage of melanoma, the quickly progressing cancer significantly diminishes their overall functioning and HRQoL. According to a qualitative, non-interventional Canadian study, the predominant physical symptom in this disease stage was exhaustion, resulting in inability to function in everyday life or participate in usual activities. Most physical impacts were perceived as severe and frequent [65]. One of the interviewed patients confirmed these findings by reporting fatigue, headaches and pain in the leg due to lymph node removal. She also describes adverse events (AEs) associated with immunotherapy, such as pain in the joints and

Alltagsleben gestaltet sich für viele Pat. schwierig

diarrhoea. Burdensome AEs were also reported by the other patient who received BRAF/MEK therapy, including fatigue, joint problems, muscle spasms, visual impairment and difficulties concentrating [66].

In emotional terms, nearly all patients reported feelings of anxiety, stress, sadness, or fear regarding their future, their families, treatment successes or failures, and the uncertainty of what lay ahead [65]. These findings were confirmed by one patient who completed the survey, who reported that anxiety is "the worst thing for me". Anxiety affects multiple aspects of her daily life: family (especially regarding her child's future), future in general, absence from and return to work, progression of the disease associated with a potential loss of successful therapy, and existential fears. A disease-specific anxiety mentioned was fearing exposure to the sun and summer. Additionally, the respondent mentioned being depressed, feeling isolated and having to deal with the loss of friends. The feeling of isolation was also described by the other patient, caused by relatives and close friends "shoving the situation away" and leaving her to manage the situation "somehow". She mentioned that there is little understanding of how demanding it is to cope with daily life and a life-threatening disease. A significant emotional point for this patient is the uncertainty: "How long will the medication be effective? When will the disease progress?" [66].

große psychische Belastung: Zukunfts- und Existenzangst, Stress, Traurigkeit

starke generelle Unsicherheit: „Wie lange wirken die Medikamente?" „Wie schnell schreitet die Erkrankung fort?"

Expectations and wishes regarding the new therapy

Expectations regarding the new therapy or a new therapy in general include prolongation of overall survival (OS): "We only want one thing, to LIVE!!!", few AEs, and prevention of relapse. The interviewed patients wish to achieve a higher quality of life (QoL) to fulfil family obligations and participate in everyday work. The chance of "getting a good medicine, regardless of who you are and where you come from" was also emphasised by the two respondents. One of the two respondents was also concerned about potential risks. She questioned whether the new therapy "only" prolongs life, or if it is also associated with an improved QoL [66].

Erwartungen an neue Therapie von den 2 befragten Pat.: Lebensverlängerung & verbesserte Lebensqualität

6.3 Further ethical and social aspects

Social impact

According to a systematic review from the US, social determinants of health, including low economic stability, government health insurance, absence of health insurance, limited educational attainment, and unmarried marital status, are to be put in context with a negative impact on melanoma survival. The authors stated that the optimal evaluation and management of patients with melanoma should therefore include an assessment of individual social determinants of health [67]. Existential fears and additional psychological stress caused by the financial situation were also mentioned by both patients participating in the survey. Since statutory sick pay is "not very high" and the payment duration is unclear, one patient's husband is even forced to work more to cover the financial burden [66]. In addition, bureaucracy (e.g. applications) is also perceived as burdensome.

individuelle soziale Determinanten sollten während der Melanom-Behandlung berücksichtigt werden

A qualitative, non-interventional Canadian study [65], conducted in 29 patients with advanced melanoma, investigated how the disease impacted their relationships, including role changes within families, support from others, and difficulties participating in social activities. Fifty-five per cent of patients noted the disruptions it caused to their daily lives within their homes, especially for those with children, the stress it caused for others, and the burden it placed on spouses and other household members to perform tasks previously handled by the patient. Although patients felt grateful for the support they had received, they also felt guilty for the perceived burden their disease caused their family and friends. Ninety-seven per cent of patients reported receiving support from others during their illness experience, and 45% reported that their relationships with family or friends had improved. While most of the discussions of social relationships were positive, 31% of patients recalled instances in which they perceived others as unsupportive (e.g. family members who did not want to discuss the illness). Despite the marked challenges of living with melanoma, 72% of the patients' spoke of efforts to "live normally" for the sake of family members, and a need to perform household chores, run errands, exercise, and raise their children. A typical pattern of impact included restricted social activity (due to being tired or out of concern for becoming exposed to contagions while immune-compromised during treatment), while still trying to attend special events (such as weddings and vacations) or maintain involvement in specific activities [65].

kanadische Studie (n=29): fortgeschrittenes Melanom belastet Familienleben – erzeugt Schuldgefühle trotz Dankbarkeit für Unterstützung

Hilfe zu erhalten, kann auch Beziehungen verbessern, 1/3 der Pat. erlebten ihr Umfeld als „nicht unterstützend"

2/3 bemühen sich um „Normalität" für die Familie, Teilnahme an Sozialleben eingeschränkt

In the US, a "TIL peer-to-peer system" has been established, matching patients who have completed TIL therapy with those undergoing or recovering from it, providing emotional and practical support [40]. In Austria, according to clinical experts, the "buddy system" of the "Österreichische Krebshilfe" could provide appropriate support [26]. The importance of such a system is supported by the findings of Egeler et al., who reported that a group of patients and partners experienced positive psychological benefits due to the social support they received from previous patients and partners who had undergone TIL therapy [68].

Unterstützung für Betroffene, z. B. österr. Krebshilfe: "Buddy System"

Autonomy, justice and equity

Informed consent, truth-telling, and confidentiality emerge from autonomy, one of the four main ethical principles [69]. Ethical considerations should be given a central role in developing TIL therapy, particularly given the severity of the disease in these patients. This includes ensuring informed consent, balancing risks and benefits, and safeguarding the patient's autonomy. Continuous ethical review and active stakeholder engagement are required to address emerging ethical dilemmas and to ensure that patient welfare remains the highest priority [64].

Autonomie der Pat. sollte sichergestellt werden

Although the one-time delivery of a TIL therapy would be convenient for patients and clinicians, as described above, the administration of lifileucel requires significant preparations and sophisticated healthcare infrastructure, which affects treatment accessibility and utilisation [30]. Access disparities may arise based on geographic, socioeconomic, and institutional factors. Addressing these disparities is crucial to ensure that all patients who could benefit from this treatment can receive it, regardless of their background or location [64]. One of the interviewed patients also emphasised this: "getting a good medicine, regardless of who you are and where you come from".

Zugang zur Behandlung sollte für alle geeigneten Pat. möglich sein, unabhängig von geografischen oder sozioökonomischen Umständen

Regarding fairness and equity, the criteria for selecting patients for TIL therapy may raise ethical concerns. It is essential to ensure that selection criteria are transparent, evidence-based, and designed to maximise benefits while minimising potential risks. It is also crucial to consider how these criteria may exclude specific populations and explore methods to make the therapy more accessible to a broader range of patients. Ensuring that TIL therapy conforms with all necessary regulations while focusing on patient safety and treatment efficacy is challenging, but essential. Streamlining these processes without compromising ethical standards could provide faster and broader access to TIL therapy [64].

transparente und evidenzbasierte Selektionskriterien notwendig

6.4 Registries and documentation of application

Although attempts have been made for several years [26], currently there is no dedicated Austrian clinical registry for melanoma. Data on this disease may be collected within general cancer registries, including the Austrian National Cancer Registry, the Austrian Brain Tumour Registry, the Tyrol Cancer Registry and the Federal State Salzburg Tumour Registry.

kein spezifisches Melanom-Register in Österreich

In Germany, annual reports of certified skin cancer centres are available, including detailed number of skin cancer cases, histologic types, disease stages and their distribution, and shifts within stages [70]. At the European level, the European Melanoma Registry (EUMelaReg) collects and evaluates real-world data on melanoma and other types of skin cancer from patients in 18 European countries; Austria is currently not participating in EUMelaReg [71].

Deutsche Krebsgesellschaft: detaillierte Melanomzahlen; EUMelaReg auf europäischer Ebene

7 Development costs and public contributions

7.1 Own development costs, acquisitions and licences

Übersicht zu Entwicklungskosten

Table 7-1 provides a summary of key information on lifileucel. Iovance Biotherapeutics has not published the total amount of research and development expenses attributed to lifileucel.

Table 7-1: AMTAGVI® overview

Originator	Developer	Information on acquisitions	Public contribution	Type of public funding
Amtagvi® Active substance: Lifileucel				
Genesis Biopharma	Iovance Biotherapeutics	Patent deal 2011: Genesis Biopharma licensed patents from the NCI for the development of Lifileucel Acquisition in 2013: Iovance Therapeutics acquired Genesis Biopharma	Basic and preclinical research primarily funded by the National Cancer Institute from 1999 to 2024	Basic, preclinical and clinical research

Abbreviation: NCI … National Cancer Institute

Basic research and clinical development

Entwicklungsgeschichte von Lifileucel

The development of lifileucel for nonresectable melanoma emerged primar-ily from public research institutions, as shown in Chapter 7 in the Appendix. Basic research on tumour-infiltrating lymphocyte (TIL) for the treatment of melanoma began in public institutions in the late 1990s at the United States (US)-funded National Cancer Institute (NCI). Several researchers and research institutes made significant contributions to the development: Steven Rosenberg (NCI) developed a process where TILs are extracted from the patient's tumour tissue, expanded to considerable quantities in the laboratory, and then reinfused into the patient to target and eliminate cancer cells. Michael Nishimura (Loyola University Chicago) built on the findings from Rosenberg and continued developing the process of extracting cells from the tumour for subsequent isolation and expansion of immune cells. The University of Pittsburgh has focused on skin cancer relevant to TIL from 2008 onwards and has played a significant part in the research. Several researchers at H. Lee Moffitt Cancer Center & Research Institute further deepened the understanding of mechanisms of action (MOA) such as understanding the function of cluster differentiation 4 (CD4), cluster differentiation 8 (CD8), programmed cell death 1 (PD-1) or cytotoxic T-lymphocyte antigen 4 (CTLA-4).

parallele Forschung und Entwicklung in den Niederlanden

Parallel to researchers in the US, several research institutes in Europe, especially in the Netherlands, conducted studies on TILs. Building on Rosenberg and colleagues' findings, in the Dutch equivalent to the NCI, the Netherlands Cancer Institute (NKI), John Haanen conducted basic, as well as late-stage clinical development of TILs, namely the M14TIL clinical trial (conducted by NKI, the Copenhagen University Hospital at Herlev, and the University of Manchester). Additionally, Leiden University conducted phase I/II studies on TILs.

Übersicht klin. Studien

The initial clinical trial for lifileucel was conducted (and sponsored) by Iovance Biotherapeutics in 2015 (NCT02360579) at publicly funded and non-governmental organizations including the H. Lee Moffitt Cancer Center and Research Institute, Providence Cancer Center Oncology and the University of Pittsburgh. The research sites included both public and private institutions, with a significant presence of academic medical centres and public hospitals across North America and Europe. Currently, there are six ongoing clinical trials using TILs conducted by Iovance Biotherapeutics (NCT03645928, NCT05361174, NCT05727904, NCT06566092, NCT06940739, NCT05398640). Six further clinical trials where Iovance Biotherapeutics is the collaborator and not the primary sponsor are currently either completed or ongoing (NCT03449108, NCT06190249, NCT05607095, NCT05640193, NCT05176470, NCT04111510). We visualised the development milestones in Figure 7-1.

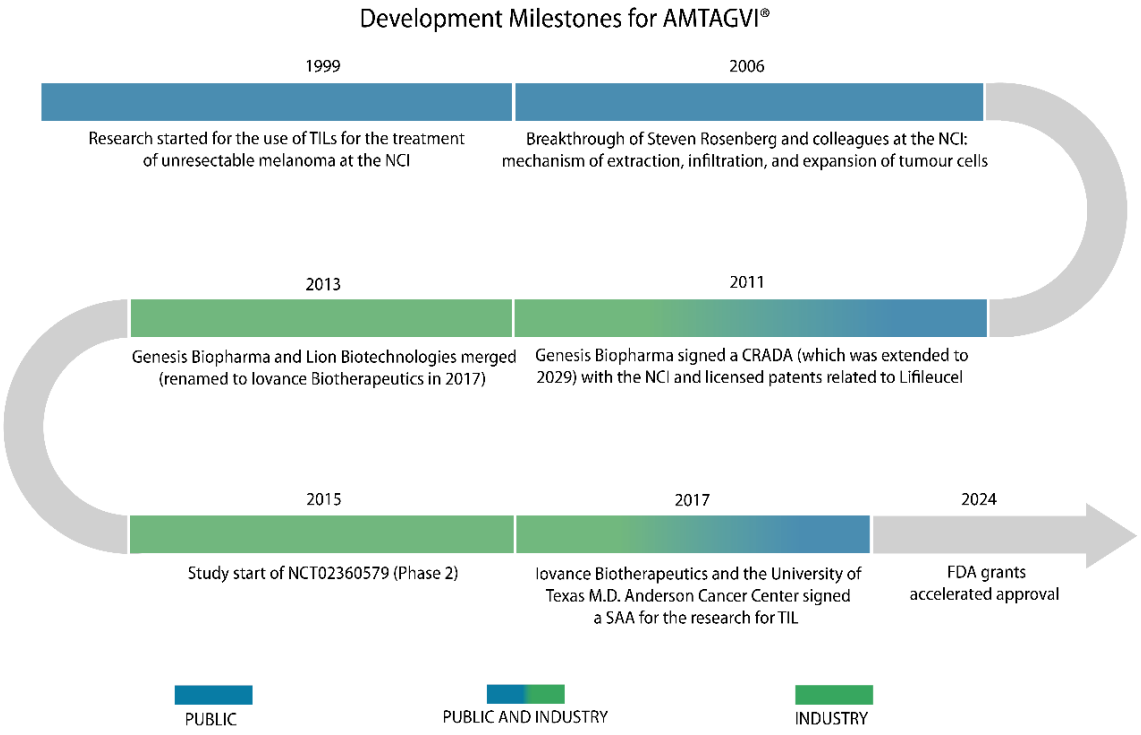


Figure 7-1: Development milestones for AMTAGVI®

7.2 Public contributions to drug development

$ 115 Millionen an öffentlichen Beiträgen identifiziert

Chapter 7 in the Appendix demonstrates substantial direct and indirect public research funding for the research on TILs. We found a total of $115.2 million (€100.2 million) in direct and indirect public funding for TIL at all stages of development. All the funding that we found came from the NCI. Research directly at the NCI amounted to roughly $57 million (€49.6 million; $24.9

million/€21.6 million for the University of Pittsburgh, $15.9 million/€13.8 million for Loyola University Chicago and $6.2 million/€5.4 million to the H. Lee Moffitt Cancer Center & Research Institute). The remaining $11 million (€9.6 million) in public funding was for the University of Texas M.D. Anderson Cancer Center, Yale University, University of Southern California, Fred Hutchinson Cancer Research Center, University of Chicago and Trampoline Pharma. The only project-specific Dutch expenses for the research for TILs are from the Innovationsfonden of DKK (Danish krone) 4.3 million (€576.500).

von öffentlicher Forschung zur Industrie

The NCI conducted pivotal basic research on TIL as early as 1999. The research on the topic has only gone more in-depth over the years with involvement in preclinical and clinical development. Industry interest spiked after the breakthrough of Steven Rosenberg on the mechanism of extraction, infiltration and expansion of tumour cells. In August 2011, Genesis Biopharma (which later merged with Iovance Biotherapeutics) signed a five-year Cooperative Research and Development Agreement (CRADA) with the NCI, which has been continuously extended to 2029. Iovance Biotherapeutics has acquired rights and patents related to lifileucel from the NCI: Patent license agreements, which require quarterly payments to the National Institutes of Health (NIH), royalty payments based on a percentage of net sales (estimated to be less than one percent to low single digit percentage), as well as milestone payments. In 2017, Iovance Biotherapeutics formed a Strategic Alliance Agreement (SAA) with the University of Texas M.D. Anderson Cancer Center. It entails funding for clinical and preclinical research of $14.2 million from Iovance Biotherapeutics (€12.3 million) with all related intellectual property rights (IPR) from the studies directly going to Iovance Therapeutics. Iovance Biotechnologies has additional partnerships with the H. Lee Moffitt Cancer Center & Research Institute, Yale University and Cellectis.

Company structure and financials

Unternehmensgeschichte geprägt durch Fusionen

The company was founded as “Freight Management Corp.” in 2007, focusing on the shipping/freight industry. The company merged with Genesis Biopharma, Inc. in 2010 and then merged with Lion Biotechnologies in 2013. In 2017 Lion Biotechnologies changed its name to Iovance Biotherapeutics. A strategic patent acquisition of Iovance Biotherapeutics was undertaken in 2023: rights to Proleukin® (interleukin-2) were acquired for £166.7 million (€195 million) with additional milestone payments from Clinigen Limited (which acquired rights to Proleukin® itself in 2019).

geschätzte Exklusivität bis 2042

From Freight Management Corp. to Iovance Biotherapeutics, Venture Capital (VC) played a pivotal role in financing the company. Iovance Biotherapeutics owns over 250 patents pertaining to lifileucel or other TIL-related technology, which leads the company to assume exclusivity until 2042.

This history of lifileucel shows progression from publicly funded basic research to industry cooperation in early-stage clinical development and continuous cooperation between industry and public research institutes until market authorisation. We can conclude that lifileucel is the result of publicly funded research that led to industry cooperation.

8 Landscape overview

8.1 Ongoing studies on lifileucel

Three ongoing clinical studies evaluating lifileucel treatment in melanoma patients and one expanded access protocol were identified via ClinicalTrials.gov [72]. The clinical studies are planned to be completed in November 2025, March 2028 and August 2029. The Marketing Authorisation Holder (MAH) sponsors two trials and the expanded access protocol, while the University of Kansas Medical Center sponsors the third trial. Detailed information about the ongoing studies is presented in Chapter 8 in the Appendix.

3 laufende Studien und 1 erweitertes Protokoll identifiziert

As of 7 May 2025, no complete HTA reports are available for lifileucel in the treatment of melanoma. The National Institute for Health and Care Research (NIHR) has issued an initial technology briefing but has not yet completed a full assessment [73]. In addition, an HTA assessment is currently in progress by the National Institute for Health and Care Excellence (NICE) and is to be completed by 10 December 2025.

bis 07.Mai 2025 kein vollständiger HTA-Bericht zu Lifileucel verfügbar; bei 2 HTA-Instituten derzeit in Bearbeitung (Fertigstellung im Dezember 2025)

8.2 Treatments in development

We searched the International Horizon Scanning Initiative (IHSI) database [46] to find therapies in the pipeline for a similar indication (second line or later line for unresectable or metastatic melanoma). We found a total of 16 different therapies in the development. Based on estimated European Commission (EC) decision timelines, the therapies are expected to receive approval in the following order: tucidinostat (October 2026), KIMMTRAK® (October 2027), IMA-203 (April 2028), RAPA-201 (Juli 2029), naporafenib (August 2029), lns8801 (December 2029), imm-1-104 (May 2030) and igrelimogene litadenorepvec (October 2030). See Chapter 8 in the Appendix for details.

16 andere Therapien in der Pipeline für inoperable metastasierte Melanome

8.3 Published studies on other TIL products

Since various research groups are actively investigating tumour-infiltrating lymphocytes (TIL) cell therapies as treatments for unresectable or metastatic melanoma, we expanded our search to identify other TIL therapies recently investigated. These findings are presented in the subsequent chapters.

Überblick zu anderen TIL-Zelltherapien

Study characteristics

One phase 2 (Forget et al. 2018 [74]), two phase 3 (Rohaan et al. 2022 and Khammari et al. 2020 [57, 75]) and one retrospective clinical study (Fradely et al. 2022 [76]) were identified for the overview of other TIL therapies under development besides lifileucel. Importantly, there are differences in the TIL manufacturing method and doses of interleukin-2 (IL-2) between the studies,

Evidenz zu anderen TIL-Therapien:
1 klinische Phase 2,
2 Phase 3 und
1 retrospektive Studie

as various groups research them. The studies are characterised in Chapter 8 in the Appendix.

Study population

Stage IV melanoma was the diagnosis of the majority of patients in both the Forget et al. and Rohaan et al. studies [57, 74]. In contrast, the Khammari et al. study [75] included patients with stage III melanoma with only one invaded lymph node after complete resection. Fradley et al. study [76] included patients with stage III and IV metastatic melanoma previously treated with TIL [77-79]. The baseline characteristics of patients are detailed in Table 8-1.

Studienpopulation der 4 Studien zu anderen TIL-Produkten: Melanom Stadium III-IV

Table 8-1: Baseline demographics of participants in the selected studies

Study reference/ study type and design	Forget et al. 2018 [74]/phase-2, prospective study	Khammari et al. 2020 [75]/phase-3 prospective study		Rohaan et al. 2022 [57]/phase-3 prospective study		Fradley et al. 2022 [76]/retrospective study
Parameter	TIL therapy (n=74)	TIL therapy (n=26)	Abstention (n=23)	TIL therapy (n=84)	Ipilimumab (n=84)	TIL therapy (n=43)
Age [years], median (range)	49 (15–68)	58 (36–75)	58 (34–75)	59 (26–74)	59 (30–77)	48*
Female [n (%)]	27 (37%)	15 (58%)	7 (30%)	37 (44)	31 (37)	43
Male [n (%)]	47 (64%)	11 (42%)	16 (70%)	47 (56)	53 (63)	57
WHO performance status score [n (%)]						
0	35 (47%)	-	-	69 (82%)	70 (83%)	-
1	36 (49%)	-	-	15 (18%)	14 (17%)	-
2	3 (4%)	-	-	-	-	-
BRAF mutation status [n (%)]						
BRAF V600 mutated	29 (39%)	-	-	37 (44%)	36 (43%)	-
Disease stage [n (%)]						
Stage III	3 (4%)	-	-	2 (2%)	2 (2%)	-
Stage IV	71 (96%)	-	-	82 (98%)	82 (98%)	-
Previous systemic therapy [n (%)]	71 (96%)	-	-	75 (89%)	74 (88%)	-
Type of melanoma [n (%)]						
Cutaneous	50 (68%)	-	-	84 (100%)	84 (100%)	-
Acral	5 (7%)	-	-	-	-	-
Mucosal	3 (4%)	-	-	-	-	-
Uveal	0	-	-	-	-	-
Undetermined	16 (22%)	-	-	-	-	-

Abbreviations: n … number of participants, TIL … tumour-infiltrating lymphocyte, WHO … World Health Organisation
*Note: * mean*

Results on relative effectiveness and safety

Clinical efficacy outcomes

The clinical efficacy of TIL therapies was studied using various primary and secondary endpoints. The results for these endpoints, whether primary or secondary, are depicted in Table 8-2.

TIL-Wirksamkeit:

The study by Forget et al. [74] reported a 42% best overall response (BOR), defined as either complete response (CR) or partial response (PR), with a median overall survival (OS) of 17.3 months in patients treated with TIL. The median progression-free survival (PFS) was four months. No comparator was available for this study. The median follow-up was 74 months.

1 Phase-2 Studie:
Ansprechrate: 42 %
Median OS: 17,3 Monate
Median PFS: 4 Monate

When comparing the TIL efficacy against no treatment in the study by Khammari et al. [75], disease-free survival (DFS) was higher in the treated population (62.5%) compared to the no-treatment group (47.8%). However, this difference did not reach statistical significance. Similarly, OS was not statistically significant between these groups.

1 Phase-3 Studie:
keine statistisch signifikante Verbesserung bzgl. DSF und OS

In the study by Rohaan et al. [57], a statistically significant improvement was reported for PFS in patients treated with TIL (7.2 months) compared to those treated with ipilimumab (3.1 months). At the time of the data cut-off on June 9, 2022, the overall median follow-up was 33.0 months.

1 Phase-3 Studie:
signifikant besseres PFS verglichen mit Ipilimumab

The study by Fradley et al. [76] reported only safety outcomes. The mean follow-up was 32 months.

Table 8-2: Efficacy results for selected studies

Reference/ID	Forget et al. 2018 [74]	Khammari et al. 2020 [75]	Rohaan et al. 2022 [57]
	TIL	TIL vs Abstention	TIL vs Ipilimumab
OR (RECIST, % (95% CI))	-	-	49 (38–60) vs 21 (13–32)
SD, % (95% CI)	-	-	19 (11–29) vs 18 (10–28)
PD, % (95% CI)	-	-	29 (19–40) vs 48 (37–59)
BOR	42%	-	-
CR, % (95% CI)	11%	-	20 (12–30) vs 7% (3–15)
PR, % (95% CI)	31%	-	29 (19–40) vs 14% (8–24)
DFS, HR (95% CI; p-value)	-	62.5% vs 47.8% 0.549 (0.23–1.30; p=0.169)	-
OS, median months (95% CI), HR (95% CI; p-value)	17.3 (11.6–37.8)	70.8%[a] vs 52.2%[a] 0.5031 (0.19–1.3; p=0.148)	25.8 (18.2–not reached) vs 18.9 (13.8–32.6) 0.83 (0.54–1.27; p=NR)
PFS, median months (95% CI), HR (95% CI; p-value)	4.0 (2.9–5.8) -		7.2 (4.2–13.1) vs 3.1 (3.0–4.3) 0.50 (0.35–0.72; p<0.001)
HRQoL (mean scores on the EORTC QLQ-C15 PAL quality of life and functioning scales)			
Global quality of life, MD (95% CI; p-value)	-	-	77.4 vs 69.6 7.7 (5.1–10.4; p=NR)

Reference/ID	Forget et al. 2018 [74]	Khammari et al. 2020 [75]	Rohaan et al. 2022 [57]
	TIL	TIL vs Abstention	TIL vs Ipilimumab
Physical functioning, MD (95% CI; p-value)	-	-	82.0 vs 79.1 2.9 (1.4–4.5; p=NR)
Emotional functioning, MD (95% CI; p-value)	-	-	85.4 vs 75.7 9.7 (7.5–11.9; p=NR)
HRQoL (mean scores on the EORTC QLQ-C15 PAL symptom scales)			
Fatigue, MD (95% CI; p-value)	-	-	25.9 vs 33.8 −7.9 (−11.2– −4.6; p=NR)
Nausea and vomiting, MD (95% CI; p-value)	-	-	7.5 vs 5.9 1.6 (0.7–2.5; p=NR)
Pain, MD (95% CI; p-value)	-	-	14.3 vs 20.7 −6.4 (−9.3– −3.5, p=NR)
Dyspnea, MD (95% CI; p-value)	-	-	10.0 vs 12.4 −2.4 (−5.0–0.1; p=NR)
Insomnia, MD (95% CI; p-value)	-	-	23.6 vs 28.1 −4.5 (−7.2– −1.9; p=NR)
Appetite loss, MD (95% CI; p-value)	-	-	12.4 vs 13.5 −1.1 (−2.9–0.7; p=NR)
Constipation, MD (95% CI; p-value)	-	-	6.7 vs 7.1 −0.4 (−1.3–0.5; p=NR)

Abbreviations: BOR … best overall response, CI … confidence interval, CR … complete response, DFS … disease-free survival, EORTC QLQ-C15 PAL … European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 15 palliative care, HR … hazard ratio, HRQoL … health-related quality of life, MD … mean difference, NR … not reported, OR … objective response, OS … overall survival, PD … progressive disease, PFS … progression-free survival, PR … partial response, RECIST … Response Evaluation Criteria in Solid Tumors, SD … stable disease, TIL … tumour-infiltrating lymphocyte therapy

Note: [a] reported as percentage survival

Safety outcomes

Adverse Events (AEs) and serious adverse events (SAEs)

The safety of TIL and IL-2 was studied in all the selected studies.

TIL-Sicherheit:

In the Forget et al. study [74], in addition to Grade 3 AEs depicted in Table 8-3, five cases of Grade 4 adverse events were reported, including fatigue, febrile neutropenia, dyspnoea and encephalopathy.

1 Phase-2 Studie:
unerwünschte Ereignisse (UE) Grad III–IV

The Khammari et al. study [75] reported AEs per the preferred term and detailed them in the publication. Overall, 31 serious AEs (SAEs) were reported for 20 patients, of which 13 were in the TIL group and seven in the comparative group. Of 31 SAEs, eight were considered related to TIL and IL-2, including the reactivation of the human herpes virus-6. IL-2 was suspected of having caused pulmonary embolism and hypereosinophilia in two patients. As only overall adverse event data were available in this study, individual adverse events are not presented in Table 8-3.

1 Phase-3 Studie:
31 schwere UE bei 13 vs. 7 Pat.

In the Rohaan et al. study [57], one patient in the TIL group died from an arterial thromboembolism. However, this was not considered to be related to the treatment. The AEs are depicted in the Table 8-3.

1 Phase-3 Studie:
1 Todesfall durch arterielle Thromboembolie

The aim of the retrospective Fradley et al. study [76] was cardiovascular safety of TIL and IL-2 reported as the overall adverse cardiovascular event rate of 41.9%. Specifically, from the TIL treated patients, 32.6% (N=14) developed hypotension requiring treatment, 14% atrial fibrillation (N=6), and 2.3% primary troponin T elevation (N=1). As adverse events were not reported as Grade 3 or 4 adverse events, data are not presented in Table 8-3.

1 retrospektive Studie: 41,9 % kardiovaskuläre Ereignisse bei TIL + IL-2

Table 8-3: Safety results of the included studies

Study reference/ID	Forget et al. 2018 [74]	Rohaan et al. 2022 [57]	
Adverse Event	Grade 3 n (%)	TIL ≥Grade 3 n (%)	Ipilimumab ≥Grade 3 n (%)
Nausea	2 (3)	0	2 (2)
Febrile neutropenia	3 (4)	59 (74)	-
Fatigue	9 (12)	7 (9)	1 (1)
Hypophosphatemia		48 (60)	-
Diarrhoea		2 (2)	12 (15)
Rash	3 (4)	9 (11)	4 (5)
Fever		36 (45)	2 (2)
Dyspnea	2 (3)	15 (19)	-
Colitis		-	16 (20)
Creatine kinase level increased		9 (11)	-
Hypertension		11 (14)	-
Hyperbilirubinemia	8 (11)	-	-
Muscle weakness	3 (4)	-	-

Abbreviations: n … number of participants, TIL … tumour-infiltrating lymphocyte therapy

Further developments

Besides the aforementioned publications, we identified two publications that also report on next generation TIL products. One publication highlights the need for engineering TILs to improve efficacy and reduce toxicity [80], whereas the second publication gives an insight into the new designs for the next generation of TIL with greater specificity, persistence, safety, and function [81].

Weiterentwicklungen hinsichtlich Next-Generation TIL-Zelltherapien

9 Discussion

This health technology assessment (HTA) evaluated lifileucel (AMTAGVI®), a novel tumour-infiltrating lymphocyte (TIL) cell therapy, for treating patients with unresectable or metastatic melanoma who have progressed following immunotherapy. Lifileucel received US Food and Drug Administration (FDA) approval on 16 February 2024 for 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 [33]. In Europe, the European Medicines Agency (EMA) evaluation is ongoing, with decisions from the Committee for Medicinal Products for Human Use (CHMP) expected in July 2024 and European Commission (EC) approval in September 2025 for "previously treated unresectable or metastatic melanoma in adults" [32].

Lifileucel als neue TIL-Zelltherapie für fortgeschrittenes Melanom

FDA-Zulassung 2024, EMA-Entscheidung ausstehend

Based on the FDA approval, available treatment guidelines and clinical expert involvement, two research questions were defined for the Austrian context:

1. *In adult patients with unresectable or metastatic melanoma who have previously received PD-1 blocking antibody or BRAF inhibitor with or without MEK inhibitor, if BRAF V600 mutation-positive, is lifileucel more effective and safer than the current standard of care?*
2. *What are the economic, ethical, organisational and social consequences of implementing lifileucel into the Austrian healthcare system?*

2 Forschungsfragen:

1. Wirksamkeit & Sicherheit von Lifileucel vs. Standardtherapie bei vorbehandeltem Melanom

2. Implementierungsfolgen im Ö Gesundheitssystem

Unresectable or metastatic melanoma represents late-stage disease (stage III to IV) with a historically poor prognosis, where patients face limited survival expectations once they have progressed through standard immunotherapy (e.g., nivolumab plus ipilimumab) and targeted therapy options (BRAF/MEK inhibitors for mutation-positive patients). Thus, the therapeutic challenge lies in the lack of effective treatment alternatives for this heavily pre-treated population, creating an unmet medical need for alternative treatments.

Immuntherapie- bzw. BRAFi/MEKi-Versagen: Pat. mit metastasiertem Melanom haben eine schlechte Prognose und fehlende wirksame Behandlungsalternativen

Current standard therapies for this patient population vary considerably depending on patients' prior treatment history, the timing of relapse after therapy (<6 or ≥6 months after completion), and the presence of a BRAF mutation or BRAF wild-type status. In general, Austrian clinical practice follows updated guidelines, including the European consensus guideline 2024 [24], ESMO guideline 2025 [25], and German S3 guidelines 2020 (*waiting for the updated version 2025*) [13].

SoC variieren je Vorbehandlung, Ö-Praxis folgt aktuellen Leitlinien

For the effectiveness and safety analysis of lifileucel, we identified one phase 2, multicohort, multicentre, open-label, single-arm study with primary endpoint objective response rate (ORR) and a median follow-up of 27.6 months [47]. Compared to trials for standard of care (SoC) regimens, lifileucel demonstrated superior response rates with an ORR rate of 31.4% (5% complete response, 26% partial response), substantially higher than nivolumab plus relatlimab, which achieved response rates of only 9.2–12.0% at a shorter median follow-up of 13.2 months [82]. While rechallenge nivolumab plus ipilimumab showed comparable response rates of 36.1% (median follow-up not reported) [83], lifileucel's median progression-free survival (PFS) of 4.1 months in the included single-arm trial exceeded that of nivolumab plus relatlimab (2.1–3.2 months) [82], and it was superior to most rechallenge ipilimumab-containing regimens (2.8 months) [83]. The median overall survival (OS) of lifileucel of 13.9 months was higher than the median OS of 11.2 months observed

Lifileucel zeigt höhere Ansprechrate als Nivolumab+Relatlimab (31,4 % vs. 9,2–12 %), aber niedrigere als Nivolumab+Ipilimumab-Rechallenge (31,4 % vs. 36,1 %); PFS nach Lifileucel ist gegenüber beiden Vergleichsregimen überlegen, nicht aber OS im Vergleich zu Nivolumab+Relatilimab

in trials with nivolumab and ipilimumab rechallenge [83], but lower than the median OS of 14.7–17.1 months after nivolumab plus relatlimab [82]. Regarding toxicities, lifileucel's safety profile raised significant concerns, with six deaths within 30 days of infusion (four treatment-emerged but mainly related to the necessary lymphodepletion (LD) and IL-2 treatment) and frequent grade 3–4 haematologic toxicities (*no overall percentages were reported*), including thrombocytopenia, anaemia, and febrile neutropenia. This contrasts markedly with nivolumab plus relatlimab's more favourable safety profile (12.8–15.0% grade 3–4 treatment-related adverse events, no treatment-related deaths) [82], while nivolumab and ipilimumab rechallenge also showed significant safety issues with ≥ grade 3 adverse events occurring in 40.5% of the patients, but also no deaths [83]. Thus, while lifileucel may offer enhanced efficacy over some standard approaches, its substantial toxicity burden requires careful patient selection and monitoring. This is also illustrated in the ESMO-MCBS of 2/5 (no substantial benefit) due to toxicity concerns [44].

Lifileucel:
erhebliche Sicherheitsbedenken mit behandlungsbedingten Todesfällen vs.
keine Todesfälle bei Vergleichstherapien

Clinical experts emphasised that 30% response rates with lifileucel following nivolumab plus ipilimumab combination are considered favourable in this population (80% of patients receive this combination, whereas the remaining 20% often receive nivolumab plus relatlimab). The ESMO-MCBS scores provide a structured way to compare clinical benefit across treatments within advanced melanoma. Lifileucel (score 2) [44], nivolumab plus ipilimumab (score 4) [84], and nivolumab plus relatlimab (score 3) [85] indicate similar but varying levels of benefit. While comparisons are valid within this disease setting, limitations arise due to differences in study design (single arm vs randomised), patient populations, and follow-up duration. Moreover, the scores do not fully capture toxicity profiles, quality of life or real-world treatment feasibility. Overall, these scores aid in guiding treatment decisions but should be interpreted cautiously and alongside individual patient factors and clinical context. In particular, the current MCBS of lifileucel does not include the most recent results of the 5-year follow-up analysis and thus needs to be re-evaluated again.

Lifileucel 30 % Ansprechen günstig für diese Pat.

ESMO-MCBS:
Lifileucel (2), NIVO/IPI (4), NIVO/Relatlimab (3) – Vergleichslimitationen durch unterschiedliche Studiendesigns – vorsichtige Interpretation nötig

A recently accepted publication by Medina et al. (2 June 2025) describes the 5-year analysis of the included C-144-01-study (pooled analysis of cohorts 2 and 4) with a median OS for the overall population of 13.9 months (95% CI, 10.6–17.8) and a 5-year OS rate of 19.7%, and 28 patients completing five years of follow-up. The ORR was 31.4%, and the median duration of response was 36.5 months (95% CI: 8.3 to not reached). The promising results should be interpreted with caution as the limitations of this analysis are still the absence of a comparator and the various non-pre-specified subgroup analyses [51]. Besides, no quality-of-life data are still available for lifileucel.

5-J-Analyse:
OS 13,9 Monate (Rate: 19,7 %),
n=28 Pat. komplett,
keine Vergleichsgruppe,
keine Lebensqualität-Daten

The study included in this assessment (C-144-01: cohorts 2 and 4) [47] enrolled patients aged ≥18 years with unresectable or metastatic melanoma (stage IIIC/IV) who had documented disease progression following at least one prior therapy, including a PD-1-blocking antibody, with BRAF-mutated patients requiring prior BRAF/MEK inhibitor treatment. Approximately 46% of the patients had normal lactate dehydrogenase (LDH) levels (≤ upper limit of normal, ULN), 35.3% had mildly elevated levels (1-2×ULN), and 19.0% had significantly elevated LDH levels (≥2×ULN), indicating that over half of the study population had elevated LDH levels, which is an important prognostic marker indicating higher disease burden and potentially more aggressive melanoma. Key inclusion criteria required ECOG performance status 0–1 (70% ECOG 0, 30% ECOG 1 in the study), life expectancy ≥3 months, adequate organ function and cardiopulmonary reserve, and at least one resectable lesion of ≥1.5cm for lifileucel generation plus one remaining measurable target lesion. Significant exclusions included uveal melanoma, prior cellular therapy,

Einschlusskriterien:
≥18 J, Stadium IIIC/IV,
Progress nach PD-1,
ECOG 0-1,
Lebenserwartung ≥3 Mon.,
resektable Läsion ≥1,5 cm

Ausschlusskriterien:
Uvealmelanom,
Hirnmetastasen,
LDH ↑ 54,2 %,
median 3 Vortherapien,
keine Bridging-Therapie

symptomatic brain metastases, chronic steroid use, active infections, and significant cardiopulmonary abnormalities. The target population comprised patients with advanced disease who had received a median of three prior therapies, representing a heavily pretreated population. Notably, bridging therapy from tumour resection to lifileucel infusion was not permitted. This may have contributed to 17.5% of patients (33 of 189) selected for tumour harvest not receiving lifileucel, mainly due to progressive disease and death. The inclusion and exclusion criteria of the C-144-01 study are relevant when transferring the results into clinical practice and selecting patients for lifileucel therapy in the real-world setting.

Overall, no published direct or indirect comparisons were available, and we assessed the study's methodological quality as moderate due to the open-label, single-arm design, several study protocol amendments and lack of pre-specified subgroup analyses. Finally, the GRADE assessment resulted in low to very low certainty of evidence for the critical and important outcomes due to open-label design and bias issues. Therefore, high-level evidence regarding clinical outcomes is lacking, and uncertainties remain.

methodische Qualität der Studie als moderat eingestuft;
GRADE: sehr niedrige Vertrauenswürdigkeit der Evidenz

The study's applicability to Austrian clinical practice appears reasonable given its international scope across multiple US and European sites and Austria's advanced healthcare infrastructure; however, the lifileucel patient population is an advanced (unresectable stage III and stage IV) melanoma patient that has progressed on a PD1 (and BRAF/MEK if mutated) and would not apply to every Austrian melanoma patient, particularly elderly patients or those with relevant comorbidities. Furthermore, there is the requirement of sufficient capacities in the specialised cell therapy facilities that already deal with complex cellular T-cell products, such as CAR T cells, which highlights the importance of establishing adequate patient selection processes including timely referral in this rapidly progressing population. Nevertheless, lifileucel is deemed to be provided in very limited number in the first year to adequately provide access to the anticipated annual patient population in Austria without inundating the health system.

Übertragbarkeit auf Ö: internationale Daten, jedoch stringente Pat.-Selektion in der Studie vs. breitere Population in der Realität (z. B. ältere oder Pat. mit mehr Komorbiditäten)

In addition, no published health economic evaluation directly comparing lifileucel to the SoC in Austria was identified. Instead, we identified two studies comparing another TIL product to ipilimumab manufactured "in-house" by a public hospital in the Netherlands [55, 56]. Both studies demonstrated that TIL is associated with a dominant ICER (less costly, more effective). One of the identified economic analyses [56] adopted a societal perspective and thus also included non-hospital related healthcare costs, out-of-pocket expenses, homecare costs, productivity losses of patients and productivity losses as well as treatment-related travel costs of family and friends. However, these results have limited applicability as we cannot establish lifileucel equivalence to in-house produced TILs, studies used production costs rather than commercial pricing. Additionally, the current standard of care for PD-1 pretreated patients in Austria is ipilimumab/nivolumab combination, not ipilimumab monotherapy.

keine publizierte Kosteneffektivitäts-bewertung zu Lifileucel vs. Standardversorgung,

aber 2 Studien zu anderen TILs vs. Ipilimumab: dominante ICER, aber Produktionskosten statt kommerzieller Preise, veralteter Komparator

AIHTA-BIA: Lifileucel-Szenario kostet etwa doppelt so viel wie SoC-Szenario

Ergebnisse mit erheblicher Unsicherheit aufgrund fehlender Daten

Standardtherapiekosten basierten auf Expert.-Einschätzungen – Kosten möglicherweise leicht unterschätzt

verhandelter Preis und Pat.-Anzahl für Lifileucel beeinflussen Budget maßgeblich

According to the self-calculated budget impact analysis (BIA) for the Austrian context, the lifileucel scenario, including lifileucel acquisition costs, pre-treatment and post-treatment costs, is projected to cost approximately twice as much as the SoC scenario (80% of the patients in Austria receive nivolumab in combination with ipilimumab; the remaining 20% receive nivolumab plus relatlimab) when 17 patients annually receive lifileucel: €14.6 million vs €6.8 million per year. While lifileucel requires standardised pre-treatment chemotherapy/LD and post-treatment IL-2 for all patients and an extended hospital stay, standard care does not. However, the analysis results are subject to considerable uncertainty, based on several assumptions used to compensate for data unavailability. For instance, to determine the anticipated size of the target population, we used historical population estimates of foreign origin and results of long-term follow-up studies. Furthermore, the SoC costs were based on clinical estimates for this pre-treated population, specifically four 3-week cycles for NIVO+IPI and three 4-week cycles for NIVO+anti-LAG3. Thus, these costs can be slightly underestimated in patients who receive further monotherapies (e.g., additional 2 cycles of NIVO monotherapy 480mg = + € 13.728). Besides, the analysis does not consider subsequent therapies, e.g. after recurrence or relapses. Sensitivity analyses confirmed that negotiated price and actual treated population substantially influence budgetary implications, as lifileucel cost represents the most significant budget impact share. In addition, a clinical expert mentioned that after the first three years following the introduction of lifileucel, i.e. beyond the time horizon of our BIA, the market penetration could increase to as high as 40%.

erhebliche öffentliche Investition: >$115 Mio. NCI-Förderung für TIL-Forschung

öffentlich-private Kooperationen seit 2011

From a public perspective, the development of lifileucel represents a substantial public investment meriting consideration in reimbursement decisions. Over $115 million in National Cancer Institute (NCI) funding supported TIL research across various institutions, including significant investments at the NCI itself ($57 million), the University of Pittsburgh ($25 million), and Loyola University Chicago ($16 million). This public funding foundation, combined with continuous public-private collaboration through agreements such as the 2011 Cooperative Research and Development Agreement, raises important questions about appropriate pricing structures given the high commercial costs relative to publicly funded development origins.

organisatorische Herausforderungen: komplexe Herstellung (von 3–5 Wochen), Krankheitsprogression möglich (überbrückende Therapie nicht ideal),

IL-2 Therapie: Zugang zu Intensivstation erforderlich

Regarding organisational aspects, the manufacturing of lifileucel involves a complex three to five weeks centralised production process requiring tumour resection, specialised shipping, and good manufacturing practice facilities, presenting significant logistical challenges for patients with advanced, rapidly progressing melanoma who may experience disease progression or clinical deterioration during this interval. According to the clinical experts, bridging therapies from resection to lifileucel therapy are not ideal in this setting as they typically reflect highly aggressive, treatment-resistant disease with poor prognosis, further complicating patient management and treatment sequencing and therefore not representing the ideal candidates for this new TIL cell therapy. In addition, the experts emphasised that the challenging IL-2 post-treatment requires high-capacity measures, including backup monitoring and intensive care unit access [62].

Furthermore, existing Austrian cell therapy centres are already at full capacity with haematological stem cell transplantation and CAR T-cell therapies and therefore with limited capacity for TIL cell therapy. Against this background, the market introduction of lifileucel in Austria would require several preparatory steps, including establishing specialised centres with sufficient infrastructure for around 17 patients to be treated with lifileucel annually. The implementation would necessitate coordinated efforts between multidisciplinary teams, including dermatologists, surgeons, radiologists, nuclear medicine experts, transfusion medicine experts and haemato-oncologists regarding the application of cell therapies in hospital settings, ensuring adequate capacities and resources are allocated across participating institutions. In addition, comprehensive training programmes would be required, considering clarification of audiences, content, and scope [35]. The successful deployment would depend on establishing robust interdisciplinary teams capable of managing the complex treatment pathway, from initial patient selection through post-infusion care. Besides, patient involvement through information materials and support systems would be essential, potentially expanding frameworks like the Austrian "Krebshilfe" buddy system [26]. Thus, patient selection would require clear coordination protocols between specialities and present significant challenges regarding resource allocation, staff training, and inter-institutional collaboration.

Zelltherapie in Ö:

Kapazität limitiert (Infrastruktur für ~17 Pat./Jahr)

Koordination zwischen Dermatolog:innen und Onkolog:innen, Schulungsprogramme, & Pat.-Informationen notwendig

Concerning social and ethical aspects, patients with advanced melanoma face enormous emotional burdens, including anxiety, stress, and existential concerns. Despite therapeutic progress, many advanced melanoma patients experience progression with low survival rates, indicating substantial unmet need. Lifileucel could provide additional options if licensed, though ensuring equal access presents challenges given complex infrastructure requirements. Patient expectations centre on survival prolongation and quality-of-life improvement, making absent quality-of-life data particularly problematic. Ethical considerations require central roles given disease severity and intensive treatment requirements with mortality risks. Access disparities must be avoided through careful, equitable distribution consideration, while transparent, evidence-based selection criteria must ensure appropriate patient selection without systematic vulnerable population exclusion.

Melanom: hohe emotionale Belastung, ungedeckter Bedarf bei niedrigen Überlebensraten

Lifileucel weitere Option, aber Zugangs-/ Infrastruktur-Probleme, fehlende QoL-Daten & ethische Überlegungen zu Behandlungsrisiken

Besides, Austria lacks a countrywide dedicated melanoma registry, with data collected within general cancer registries. Data procurement presents significant challenges, particularly regarding population estimates, necessitating extrapolation from countries with robust systems like Germany.

kein spezifisches Melanom-Register in Ö – nur allgemeine Krebsregister vorhanden

The rationale for the two identified ongoing trials (NCT06151847 and NCT05727904) is to assess whether lifileucel, either alone in later-line settings or in combination with pembrolizumab in first-line advanced melanoma, can improve response rates and survival outcomes by directly infusing tumour-reactive T cells and harnessing checkpoint blockade synergy. Expectations include confirming the durability of responses in pretreated patients and demonstrating a potential new standard of care in first-line melanoma through enhanced efficacy versus pembrolizumab monotherapy.

laufende Studien: Lifileucel mono/kombiniert mit Pembrolizumam als Erstlinie zur Verbesserung der Melanom-Therapie

Concerning new treatments for advanced melanoma, for example, other non-commercial TIL therapies are currently under investigation. The effectiveness of these in-house produced TIL-therapies was assessed in a randomised-controlled trial comparing TIL to ipilimumab [57] next to three non-randomised studies [74-76]. The RCT presented a statistically significant improvement in PFS when comparing TIL with ipilimumab. However, the clinical relevance of this difference is questionable (7.2 vs 3.1 months), since ipilimumab monotherapy is no longer a standard of care. This study has similarly shown an increased ≥grade 3 rate of febrile neutropenia (in 74% of patients) and concluded that the TIL therapy shows promise for a specific subset of patients with advanced melanoma who have exhausted standard options, but the benefit-risk ratio should be carefully considered given the significant toxicity profile [57]. However, due to the current limitations of TIL cell therapy, particularly the high toxicity, these therapies are being constantly further developed, e.g. the next generation TILs, with the primary aim of improving their safety profiles [80, 81].

weitere Therapieoptionen für fortgeschrittenes Melanom: nicht kommerziell produzierte TILs: statistisch signifikante PFS-Verbesserung vs. IPI, aber hohe Toxizität (74 % febrile Neutropenie ≥Grad 3); TIL-Zelltherapien werden jedoch stetig weiterentwickelt (Next-Generations), um Sicherheitsprofil zu verbessern

Additionally, we found 16 different therapies in development for unresectable and metastatic melanoma, of which the earliest estimated EC decision is expected for tucidinostat in October 2026, and the latest for igrelimogene litadenorepvec in October 2030.

zusätzliche andere Therapien, darunter z. B. Tucidinostat (Zulassung im Okt. 2026 erwartet)

Overall, lifileucel represents a promising but complex therapeutic option requiring careful consideration of clinical benefit-risk profiles, substantial economic implications, and major organisational implementation challenges. Current evidence demonstrates clinically relevant benefit in heavily pretreated patients but lacks robust comparative data and quality-of-life measurements. Decision-makers must weigh medical need against significant toxicity, high costs, and substantial infrastructure requirements, and considering potential evidence evolution through ongoing clinical trials, new treatment developments and substantial public investment during lifileucel development.

Lifileucel = weitere Therapieoption mit klinischer relevanter Wirksamkeit, aber hoher Toxizität & fehlenden Vergleichsdaten → Abwägung: medizinischer Bedarf vs. erheblichen Kosten/Infrastruktur-Anforderungen

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List of abbreviations

AE ..... adverse event
AEs ..... adverse events
AIHTA ..... Austrian Institute for Health Technology Assessment
AJCC ..... American Joint Committee on Cancer
Anti-LAG 3 ..... anti-lymphocyte-activation gene 3
Anti-PD-1 ..... anti-programmed cell death protein 1
ATC ..... authorised treatment centres
ATMP ..... Advanced Therapy Medicinal Product
BLA ..... biologics license applications
BIA ..... budget impact analysis
BOR ..... best overall response
BRAF ..... v-Raf murine sarcoma viral homologue B1
BRAFi ..... v-Raf murine sarcoma viral homologue B1 inhibitor
BSC ..... best supportive care
CCIT-DK ..... Danish National Center for Cancer Immune Therapy
CD4 ..... cluster of differentiation 4
CD8 ..... cluster of differentiation 8
CE ..... cost-effectiveness
CEAC ..... cost-effectiveness acceptability curves
CED ..... Coverage with Evidence Development
CHEERS ..... Consolidated Health Economic Evaluation Reporting Standards
CHMP ..... Committee for Human Medicinal Products
CI ..... confidence interval
CR ..... complete response
CRADA ..... Cooperative Research and Development Agreement
CSD ..... cumulative sun damage
CT ..... computed tomography
CTLA-4 ..... cytotoxic T-lymphocyte antigen 4
DK ..... Danish
DNA ..... deoxyribonucleic acid
DOR ..... duration of response
DSA ..... deterministic sensitivity analysis
EADO ..... European Association of Dermato-Oncology
EC ..... European Commission
ECOG ..... Eastern Cooperative Oncology
EKO ..... refund code (Erstattungskodex)
EMA ..... European Medicines Agency
ESMO ..... European Society for Medical Oncology
ESMO-MCBS ... European Society for Medical Oncology – Magnitude of Clinical Benefit Scale
EU ..... European Union
EUnetHTA ..... European Network for Health Technology Assessment
EVPI ..... expected value of perfect information
FAMMM ..... Familial Atypical Multiple Mole and Melanoma
FDA ..... United States Food and Drug Administration
GRADE ..... grading of recommendations assessment, development and evaluation
GÖG ..... Austrian Public Health Institute (Gesundheit Österreich GmbH)
HRQoL ..... health-related quality of life
HTA ..... health technology assessment
H1 ..... histamine 1 receptor
ICER ..... incremental cost-effectiveness ratio
ICI ..... immune checkpoint inhibitor
ICIs ..... immune checkpoint inhibitors
IHE ..... Institute for Health Economics
IHSI ..... International Horizon Scanning Initiative
IL-2 ..... interleukin-2
INN ..... international non-proprietary name
IPI ..... ipilimumab
IPR ..... intellectual property rights
IRC ..... independent review committee
IV ..... intravenous
KIT ..... stem-cell factor receptor, CD117
Kr ..... Danish krone

LAG3 ..... lymphocyte-activation gene 3
LD ..... lymphodepletion
LDH ..... lactate dehydrogenase
LKF ..... Austrian diagnosis-related group system (Leistungsorientierte Krankenanstaltungfinanzierung)
MAA ..... marketing authorisation application
MAH ..... Marketing Authorisation Holder
MEK ..... mitogen-activated protein kinase kinase
MEKi ..... mitogen-activated protein kinase kinase inhibitor
MHRA ..... Medicines and Healthcare products Regulatory Agency
MO ..... month
MOA ..... mechanism of action
MRI ..... magnetic resonance imaging
MSS ..... melanoma specific survival
N ..... number of participants
NED ..... no evidence of disease
N/A ..... not available
NCCN ..... National Comprehensive Cancer Network
NCI ..... National Cancer Institute
NF1 ..... neurofibromin 1
NICE ..... National Institute for Health and Care Excellence
NIH ..... National Institutes of Health
NIHR ..... National Institute for Health and Care Research
NMB ..... net monetary benefit
NIVO ..... nivolumab
NKI ..... Netherlands Cancer Institute
NL ..... Netherlands
N/R ..... not reached
NR ..... not reported
NRAS ..... neuroblastoma rat sarcoma viral oncogene homologue
ORR ..... objective response rate
OS ..... overall survival
PD ..... progressed disease
PD-1 ..... programmed cell death protein 1
PD-L1 ..... programmed death ligand 1
PET ..... positron emission tomography
PFS ..... progression-free survival
PICO ..... patient. intervention, comparison and outcome
PR ..... partial response
PRIME ..... Priority Medicines
PRISMA ..... preferred reporting items for systematic reviews and meta-analyses
pT1b ..... pathologic tumour stage 1b
Q ..... every
QALY ..... quality-adjusted life-year
QALYs ..... quality-adjusted life-years
QoL ..... quality of life
RECIST ..... response evaluation criteria in solid tumors
RCTs ..... randomised controlled trials
RNA ..... ribonucleic acid
SAEs ..... serious adverse events
SD ..... stable disease
SoC ..... standard of care
S100B ..... S100 calcium binding protein B
TEAEs ..... treatment-emergent adverse events
TGA ..... Therapeutic Goods Administration
TIL ..... tumour-infiltrating lymphocyte
TNF ..... tumour necrosis factor
TNM ..... tumour, node, metastasis
UK ..... United Kingdom
US ..... United States
UV ..... ultraviolet
VOI ..... value of information
WHO ..... World Health Organisation
WT ..... wild type
WTP ..... willingness-to-pay

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH