HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

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

HTA-Appendix

Appendix

Decision Support Document for the Austrian Appraisal Board 004 | ISSN online: 1998-0469
AIHTA. Vienna, 01.08.2025

Project Team

Project leader:	Sarah Wolf, MSc
AIHTA Appraisal Board Author Group:	Alba Colicchia, BSc MPH
	Daniel Fabian, MSc
	Dr. MMag. Sabine Geiger-Gritsch
	Naomi Linton-Romir, MPH, BSc
	PharmDr. Eva Malíková, PhD
	Michaela Riegelnegg, BSc MA
	Dr. med. Eleen Rothschedl
	Ozren Sehic, MA, MSc
	Diana Szivakova, MA
	Priv.-Doz. Dr. phil. Claudia Wild
	Sarah Wolf, MSc

Project Support

Systematic literature search: Tarquin Mittermayr, BA(Hons)

External review: ao. Univ.-Prof. Dr. Christoph Höller from the Medical University of Vienna,
Univ.-Prof. Dr. Dominik Wolf from the Medical University of Innsbruck

Internal review: Dr. MMag. Sabine Geiger-Gritsch

Correspondence: HTA-Austria Appraisal Board Team, bewertungsboard@aihta.at

This report should be referenced as follows:

AIHTA-Appraisal Board Author Group. Lifileucel (AMTAGVI®) for previously treated unresectable or metastatic melanoma. Decision Support Document for the Austrian Appraisal Board 004; 2025. Vienna: HTA Austria – Austrian Institute for Health Technology Assessment GmbH.

Conflict of interest

All authors and the reviewers involved in the production of this report have declared they have no conflicts of interest in relation to the technology assessed according to the Uniform Requirements of Manuscripts Statement of Medical Journal Editors (www.icmje.org).

Disclaimer

The external reviewers did not co-author the scientific report and do not necessarily all agree with its content. Only the AIHTA is responsible for errors or omissions that could persist. The final version and the policy recommendations are under the full responsibility of the AIHTA.

IMPRINT

Publisher:
HTA Austria – Austrian Institute for Health Technology Assessment GmbH
Josefstädter Str. 39 | 1080 Vienna – Austria
https://www.aihta.at/

Responsible for content:
Dr. rer. soc. oec. Ingrid Zechmeister-Koss, managing director

Decision Support Document for the Austrian Appraisal Board do not appear on a regular basis and serve to publicize the research results of the Austrian Institute for Health Technology Assessment.

Decision Support Document for the Austrian Appraisal Board are only available to the public via the Internet at http://eprints.aihta.at/view/types/hta_report.html.

Decision Support Document for the Austrian Appraisal Board No.: 004 ISSN online 1998-0469

Content

List of tables

List of figures

1 Introduction

1.1 Disease background

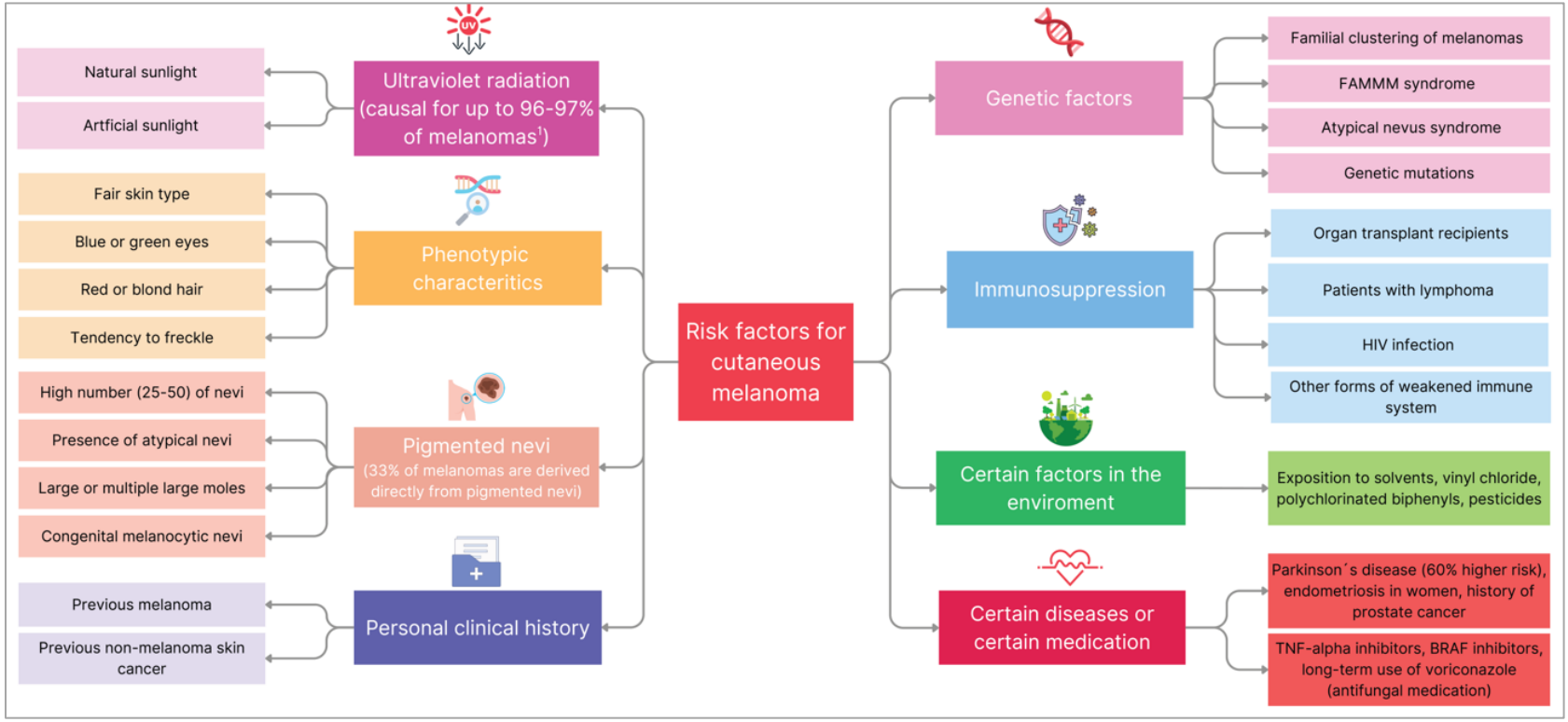


Figure 1- 1: Main risk factors for the development of melanoma (Figure created with CANVA.)
Note: information from [1-3]

Abbreviations: BRAF…V-Raf Murine Sarcoma Viral Oncogene Homologue B, FAMMM syndrome…Familial Atypical Multiple Mole and Melanoma Syndrome, HIV…human immunodeficiency virus, TNF…tumour necrosis factor.

[1]Worldwide, the percentage of melanomas attributed to ultraviolet radiation is estimated at around 75%, but in Oceania, the US and most parts of Europe, the population-attributable factor is higher, reaching 96-97% [4]

Table 1- 1: Morphological classification of the four main subtypes of cutaneous melanoma. Adapted from [5].

Feature	Superficial Spreading Melanoma	Nodular Melanoma	Lentigo Maligna Melanoma	Acral Lentiginous Melanoma
Frequency	70% of all melanomas	15-30% of all melanomas	10-15% of all melanomas	<5% of all melanomas (approx. 75% in non-white individuals)
Location	Can occur anywhere; predilection for the back in males and females and lower extremities in females	Can occur anywhere	Chronically sun-damaged areas in older individuals	Palmar, plantar, and subungual surfaces (beneath the nail plate)
Appearance	Variably pigmented macule or thin plaque with irregular border; few mm to several cm in diameter; multiple shades (brown, red, blue, black, grey, white)	Darkly pigmented, pedunculated, or polypoid papules/nodules; often uniform colour or amelanotic/pink hue; symmetric borders; relatively small diameter	Begins as a tan or brown macule; gradually enlarges over the years; develops darker, asymmetric foci of pigmentation, colour variegation, and raised areas	Dark brown to black, irregularly pigmented macules or patches; raised areas, ulceration, bleeding, and/or larger diameter indicating deeper invasion
Thickness/ Prognosis	>60% diagnosed at ≤1 mm thickness (highly curable)	Most >2 mm at diagnosis	Slow-growing, beginning as in situ melanoma ("lentigo maligna")	Often diagnosed at later stages

Table 1- 2: Overview of cutaneous melanoma stage I-III following the American Joint Committee on Cancer (AJCC) TNM: tumour (T), regional lymph nodes (N), and distant metastasis (M). Adapted from [4]

Substage	Primary tumour characteristics	Lymph node involvement	Distant metastasis
IA	<0.8 mm thick without ulceration	No lymph node involvement	No distant metastasis
IB	▪ <0.8 mm thick with ulceration, OR ▪ 0.8-1.0 mm thick with or without ulceration, OR ▪ >1.0-2.0 mm thick without ulceration	No lymph node involvement	No distant metastasis
IIA	▪ 1.01-2.0 mm thick with ulceration, OR ▪ 2.01-4.0 mm thick without ulceration	No lymph node involvement	No distant metastasis
IIB	▪ 2.01-4.0 mm thick with ulceration, OR ▪ >4.0 mm thick without ulceration	No lymph node involvement	No distant metastasis
IIC	▪ >4.0 mm thick with ulceration	No lymph node involvement	No distant metastasis
IIIA	▪ >1 mm thick with ulceration, OR ▪ ≤2 mm thick without ulceration	Cancer found in 1-3 lymph nodes by sentinel lymph node biopsy	No distant metastasis
IIIB	▪ No sign of primary tumor, OR ▪ >1 mm thick with ulceration, OR ▪ ≤2 mm thick without ulceration, OR ▪ >2-4 mm thick with ulceration, OR	Cancer found in 1-3 lymph nodes by physical exam or imaging tests	▪ May have microsatellite tumours, satellite tumours, and/or in-transit metastases on or under the skin ▪ No distant metastasis

Substage	Primary tumour characteristics	Lymph node involvement	Distant metastasis
	▪ >4 mm thick with ulceration		
IIIC	▪ No sign of primary tumour, OR ▪ >2 mm thick with/without ulceration, OR ▪ ≤4 mm thick without ulceration, OR ▪ >2-4 mm thick with ulceration, OR ▪ >4 mm thick with ulceration	Cancer found in 1-4+ lymph nodes or matted lymph nodes	▪ May have microsatellite tumours, satellite tumours, and/or in-transit metastases on or under the skin ▪ No distant metastasis
IIID	▪ >4 mm thick with ulceration	▪ Cancer found in 4+ lymph nodes or matted lymph nodes, OR ▪ Cancer found in 2+ lymph nodes/matted lymph nodes	▪ May have microsatellite tumours, satellite tumours, and/or in-transit metastases on or under the skin ▪ No distant metastasis

Table 1- 3: Overview of cutaneous melanoma stage IV

Metastatic category	Site of Metastasis	LDH Level Subcategories	Description
M1a	Distant skin, soft tissue including muscle, and/or distant lymph nodes	▪ M1a(0): LDH not elevated ▪ M1a(1): LDH elevated	Metastasis to skin sites far from original tumour, soft tissues, and/or lymph nodes not near the original site
M1b	Lungs	▪ M1b(0): LDH not elevated ▪ M1b(1): LDH elevated	Metastasis to the lungs (with or without M1a sites of disease)
M1c	Internal organs	▪ M1c(0): LDH not elevated ▪ M1c(1): LDH elevated	Metastasis to internal organs such as liver, digestive tract, etc. (with or without M1a or M1b sites of disease)
M1d	Central nervous system	▪ M1d(0): LDH not elevated ▪ M1d(1): LDH elevated	Metastasis to brain, spinal cord, or other parts of the central nervous system (with or without M1a, M1b, or M1c sites of disease)

Stage IV melanoma is characterised by the presence of distant metastasis, regardless of primary tumour characteristics. Unlike earlier stages, stage IV classification relies entirely on the 'M' component of the TNM system. Each M category is further subdivided based on lactate dehydrogenase (LDH) serum levels. Adapted from [4].

1.2 Standard of care in Austria

Table 1- 4: Overview of treatment approaches for unresectable and metastatic melanoma and their descriptions

Abbreviation	Treatment	Agent	Description
Immune checkpoint inhibitors			
Anti-PD-1	Anti-programmed cell death protein 1	Nivolumab	PD-1 checkpoints are blocked to enhance the immune response by allowing T cells, a key component of the immune system, to more effectively attack cancer cells [3].
Anti-CTLA-4	Anti-Cytoxic T-lymphocyte-associated antigen 4	Ipilumumab	CTLA-4 checkpoints are blocked to enhance the immune response by allowing T cells to attack cancer cells better [6].
Anti-LAG-3	Anti-Lymphocyte-activation gene 3	Relatlimab	LAG-3 checkpoints are blocked to enhance the immune response by allowing T cells to attack cancer cells better [6].
Other treatments			
BRAFinhibitor	V-raf murine sarcoma viral oncogene homologue B1 inhibitor	Dabrafenib	BRAFi targets BRAF enzymes to block cancer growth in cancers with BRAF mutations [8].

MEK-inhibitor	Mitogen-activated protein kinase inhibitor	Trametinib	MEKi targets MEK enzymes to block cancer growth in cancers in cancers with BRAF mutations [7].
TIL	Tumour-infiltrating lymphocyte	Lifileucel	The HTA report focuses on this treatment.

Table 1- 5: Standard dosing and administration frequencies of therapeutic agents employed in Austria following disease progression after initial treatment [8]

Agent of therapy	Dosage/frequency of use
Combination therapy: Anti-PD-1 + Anti-CTLA-4-based immunotherapy	
Nivolumab	1 mg/kg every 3 weeks for 4 cycles
Ipilimumab	3 mg/kg every 3 weeks for 4 cycles
Combination therapy: Anti-PD-1 + Anti-LAG3-based immunotherapy	
Nivolumab plus	480 mg every 4 weeks for a median of 3 cycles
Relatlimab-rmbw	160 mg every 4 weeks for a median of 3 cycles
Monotherapy: Anti-CTLA-4-based immunotherapy	
Ipilimumab monotherapy, only in rare cases	3 mg/kg every 3 weeks for a total of 4 doses
Combination therapy: BRAF inhibitor + MEK inhibitor	
Dabrafenib (, L01EC02)	150 mg twice daily (daily max dose of 300 mg) until no effectiveness or toxicity
Trametinib (, L01EE01)	2 mg once daily until no effectiveness or toxicity
Combination therapy: BRAF inhibitor + MEK inhibitor	
Encorafenib (, L01EC03)	450 mg (6 caps of 75 mg) once daily until no effectiveness or toxicity
Binimetinib (, L01EE03)	45 mg (3 caps of 15 mg) twice daily every 12h, max dose of 90 mg until no effectiveness or toxicity

Abbrevations: Anti-PD-1…Anti-programmed cell death protein 1…Anti-CTLA-4-…Anti-Cytoxic t-lymphocyte-associated antigen 4…Anti-LAG3…Anti-Lymphocyte-activation gene 3.

Note: BRAF inhibitors and MEK inhibitors are primarily administered as combination therapy in Austrian clinical practice, though monotherapy remains a viable option in select cases. Notably, the recommended dosages remain consistent whether these agents are used individually or in combination.

1.3 Medicinal product under evaluation

The manufacturer comments on the patent expiry of the active ingredient in Europe as follows: "Iovance currently owns more than 230 granted or allowed U.S. and international patents and patent rights for Amtagvi and other TIL-related technologies that are expected to provide Amtagvi with exclusivity through at least 2042. This patent portfolio covers TIL compositions and methods of treatment and manufacturing in a broad range of cancers, with Gen 2 patent rights expected to provide exclusivity for Amtagvi into 2038 and additional patent rights, including methods of treating melanoma and compositions and methods for potency assays, expected to provide exclusivity into 2039 and 2042, respectively. Iovance also owns an industry-leading patent portfolio covering TIL products produced with genetic engineering, using core biopsies and peripheral blood as starting material, and using combinations of TIL products with checkpoint inhibitors, as well as Iovance's proprietary IovanceCares™ system."

2 Scope of assessment

No additional tables or figures are provided for this chapter.

3 Methods

Systematic literature search

Cochrane (07.05.2025)

ID Search

#1 (lifileucel*) (Word variations have been searched)

#2 (amtagvi*) (Word variations have been searched)

#3 (contego*) (Word variations have been searched)

#4 (ln NEXT 144*) (Word variations have been searched)

#5 (ln-144*) (Word variations have been searched)

#6 (ln?144*) (Word variations have been searched)

#7 (ln NEXT 145*) (Word variations have been searched)

#8 (ln-145*) (Word variations have been searched)

#9 (ln?145*) (Word variations have been searched)

#10 ((tumo*r* NEXT infiltr* NEXT lymphocyte* OR TIL*) NEAR (therap* OR immuno*therap* OR immuno-therap*)) (Word variations have been searched)

#11 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

#12 MeSH descriptor: [Melanoma] explode all trees

#13 (melanoma*) (Word variations have been searched)

#14 ((skin OR cutaneous OR derma*) NEAR (cancer* OR tumo*r* OR carcinom* OR adenom* OR adeno*c* OR sarcoma* OR neoplasm* OR malignan*)) (Word variations have been searched)

#15 #12 OR #13 OR #14

#16 #11 AND #15

#17 (conference proceeding):pt

#18 (abstract):so

#19 (clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so

#20 #17 OR #18 OR #19

#21 #16 NOT #20

27 Hits

Embase (07.05.2025)

No. Query

#18. #16 NOT #17

#17. #16 AND 'Conference Abstract'/it

#16. #11 AND #15

#15. #12 OR #13 OR #14

#14. (skin* OR cutaneous OR derma*) NEAR/2 (cancer* OR tumo*r* OR carcinom* OR adenom* OR adeno*c* OR sarcoma* OR neoplasm* OR malignan*)

#13. melanoma*

#12. 'melanoma'/exp

#11. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

#10. ('tumo$r* infiltr* lymphocyte*' OR til*) NEAR/2 (therap* OR immuno$therap* OR 'immuno-therap*')

#9. 'til therapy'/exp

#8. ln145*

#7. 'ln 145*'

#6. ln144*

#5. 'ln 144*'

#4. contego*

#3. amtagvi*

#2. lifileucel*

#1. 'lifileucel'/exp

International HTA database (07.05.2025)

Search step # Search query,"Hits","Searched At"

16 (((skin OR cutaneous OR derma*) AND (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR sarcoma* OR neoplasm* OR malignan*)) OR (melanoma*) OR ("Melanoma"[mhe])) AND (("Lymphocytes Tumor-Infiltrating"[mhe]) OR (TIL) OR ("tumor infiltrating lymphocyte immunotherapy" OR "tumor infiltrating lymphocyte therapy" OR "tumor infiltrating lymphocytes therapy" OR "tumour infiltrating lymphocyte immunotherapy" OR "tumour infiltrating lymphocyte therapy" OR "tumour infiltrating lymphocytes therapy" OR "TIL therapy") OR (ln145*) OR ("ln 145") OR (ln144*) OR ("ln 144") OR (contego*) OR (amtagvi*) OR (lifileucel*)),"0","2025-04-23T14:26:29.000000Z"

15 ((skin OR cutaneous OR derma*) AND (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR sarcoma* OR neoplasm* OR malignan*)) OR (melanoma*) OR ("Melanoma"[mhe]),"334","2025-04-23T14:26:09.000000Z"

14 (skin OR cutaneous OR derma*) AND (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR sarcoma* OR neoplasm* OR malignan*),"156","2025-04-23T14:25:17.000000Z"

13 melanoma*,"209","2025-04-23T14:23:41.000000Z"

12 "Melanoma"[mhe],"178","2025-04-23T14:23:29.000000Z"

11 ("Lymphocytes Tumor-Infiltrating"[mhe]) OR (TIL) OR ("tumor infiltrating lymphocyte immunotherapy" OR "tumor infiltrating lymphocyte therapy" OR "tumor infiltrating lymphocytes therapy" OR "tumour infiltrating lymphocyte immunotherapy" OR "tumour infiltrating lymphocyte therapy" OR "tumour infiltrating lymphocytes therapy" OR "TIL therapy") OR (ln145*) OR ("ln 145") OR (ln144*) OR ("ln 144") OR (contego*) OR (amtagvi*) OR (lifileucel*),"36","2025-04-23T14:23:15.000000Z"

10 "Lymphocytes Tumor-Infiltrating"[mhe],"0","2025-04-23T14:22:58.000000Z"

9 TIL,"2","2025-04-23T14:21:14.000000Z"

8 "tumor infiltrating lymphocyte immunotherapy" OR "tumor infiltrating lymphocyte therapy" OR "tumor infiltrating lymphocytes therapy" OR "tumour infiltrating lymphocyte immunotherapy" OR "tumour infiltrating lymphocyte therapy" OR "tumour infiltrating lymphocytes therapy" OR "TIL therapy","0","2025-04-23T14:20:44.000000Z"

7 ln145*,"0","2025-04-23T14:13:37.000000Z"

6 "ln 145","18","2025-04-23T14:13:18.000000Z"

5 ln144*,"0","2025-04-23T14:12:35.000000Z"

4 "ln 144","16","2025-04-23T14:12:20.000000Z"

3 contego*,"0","2025-04-23T14:11:50.000000Z"

2 amtagvi*,"0","2025-04-23T14:11:30.000000Z"

1 lifileucel*,"0","2025-04-23T14:11:02.000000Z"

Medline (07.05.2025)

1 lifileucel*.mp.

2 amtagvi*.mp.

3 contego*.mp.

4 ln 144*.mp.

5 ln144*.mp.

6 ln 145*.mp.

7 ln145*.mp.

8 ((tumo?r* infiltr* lymphocyte* or TIL*) adj3 (therap* or immuno?therap* or immuno-therap*)).mp.

9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

10 exp Melanoma/

11 melanoma*.mp.

12 ((skin or cutaneous or derma*) adj3 (cancer* or tumo?r* or carcinom* or adenom* or adeno?c* or sarcoma* or neoplasm* or malignan*)).mp. (176992)

13 10 or 11 or 12

14 9 and 13

14 remove duplicates from 14

National Library of Medicine (PubMed) search for economic evaluation studies

"Lymphocytes, Tumor-Infiltrating"[Mesh] AND "Health Care Costs"[Mesh]

"Lymphocytes, Tumor-Infiltrating"[Mesh] AND "Cost-Benefit Analysis"[Mesh] AND "Melanoma"[Mesh]

Study selection – PRISMA flow chart

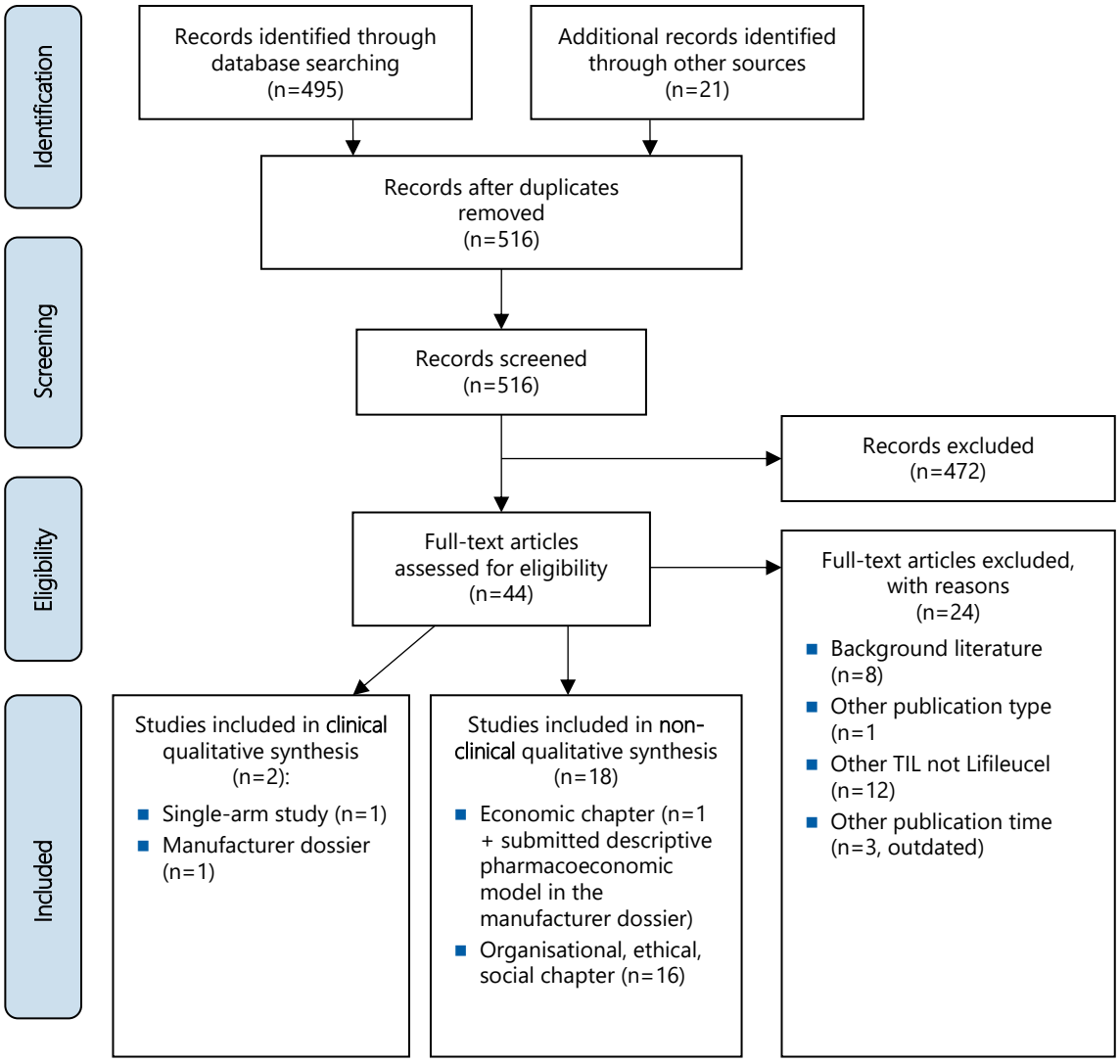


Figure 3- 1: Flow chart of study selection (PRISMA flow diagram)

4 Clinical effectiveness and safety

4.1 Characteristics of included studies

Table 4- 1: Baseline demographics and disease characteristics of participants in the Chesney et al. study

Study reference/ID Characteristics Category	Study intervention		
C-144-01 Trial [9]	**Cohort 2 (n=66)**	**Cohort 4 (n=87)**	**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)
Melanoma subtype, n (%)			
Cutaneous	39 (59.1)	44 (50.6)	83 (54.2)
Mucosal	4 (6.1)	8 (9.2)	12 (7.8)
Acral	4 (6.1)	6 (6.9)	10 (6.5)
Melanoma of other subtypes (unknown primary subtype or insufficient information)	-	-	47 (30.7)
BRAF V600-mutated, n (%)	17 (25.8)	24 (27.6)	41 (26.8)
PD-L1 status, n (%)			
TPS ≥1%	37 (56.1)	39 (44.8)	76 (49.7)
TPS <1%	12 (18.2)	20 (23.0)	32 (20.9)
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)
Liver and/or brain lesions by IRC, n (%)	28 (42.4)	44 (50.6)	72 (47.1)
Median target lesion SOD (range), mm	95.8 (13.5-271.3)	99.5 (15.7-552.9)	97.8 (13.5-552.9)
Baseline lesions in ≥3 anatomic sites, n (%)	44 (66.7)	65 (74.7)	109 (71.2)
Baseline target and non-target lesions, n (%)			
≤3	22 (33.3)	14 (16.1)	36 (23.5)
>3	43 (65.2)	73 (83.9)	116 (75.8)
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)
Prior systemic therapies, n (%)			
Median number of therapies (range)	3.0 (1-9)	3.0 (1-8)	3.0 (1-9)
Anti-PD-1/PD-L1	66 (100)	87 (100)	153 (100)
Anti-CTLA-4	53 (80.3)	72 (82.8)	125 (81.7)

Study reference/ID Characteristics Category	Study intervention		
C-144-01 Trial [9]	**Cohort 2 (n=66)**	**Cohort 4 (n=87)**	**Cohort 2+4 (n=153)**
Anti-PD-1 plus anti-CTLA-4 combination	34 (51.5)	48 (55.2)	82 (53.6)
BRAF±MEK inhibitor	15 (22.7)	24 (27.6)	39 (25.5)
IL-2	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)
Anatomic site of resection			
Lymph node/skin/subcuta-neous	28 (42.4)	43 (49.4)	71 (46.4)
Visceral organ	12 (18.2)	30 (34.5)	42 (27.5)
Other	26 (39.4)	14 (16.1)	40 (26.1)

Abbreviations:CTLA-4…cytotoxic T-lymphocyte-associated protein 4, ECOG…Eastern Cooperative Oncology Group, IL…interleukin, IRC…independent review committee, LDH…lactate dehydrogenase, n…number of participants, PD-1…programmed cell death protein 1, PD-L1…programmed death ligand 1, SOD…sum of diameter, TPS…tumor proportion score, ULN…upper limit of normal

4.2 Results of effectiveness and safety

Table 4- 2: ESMO-MCBS Scorecard of melanoma therapies

Drug	Form	MG ST	MG	HR (95% CI)	PM	Toxicity	QoL	AJ	CS	FM
Lifileucel [10]	3	NA	ORR: 31.4% (CI 95%: 24.1-39.4)	NA	3	41.7% febrile neutro-penia grade 3-4	NA	-1	-	**2**
Ipilimumab [11]	1	Placebo, 5-year OS: 54.4%	5-year OS: 11%	0.72 (95.1% CI 0.58-0.88)	-	-	NA		A	**A**
Nivolumab + ipili-mumab [12]	2a, 1	Ipilimumab, OS: 19.9 months 10-year OS: 19%	OS: 52.2 months; 10-year OS gain: 24% (with plateau)	0.53 (0.44-0.65)	4	-	NA	-	A	**4A**
Nivolumab + relatlimab [13]	2b	Nivolumab, PFS: 4.6 months	PFS: 5.5 months	0.75 (0.62-0.92)	3	-	NA	-	-	**3**
Dabrafenib + tramet-inib [14]	2a	Dabrafenib, OS: 18.7 months, 3-year OS 32%	OS: 6.4 months, 3-year OS 11%	0.71 (0.55-0.92)	4	6% reduc-tion skin cancer	NA	+1	-	**5**
Encorafenib + Binimetinib	**ESMO-MCBS Scorecard not available**									

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

4.3 Quality of evidence

Table 4- 3: Risk of bias of the Chesney et al. study (IHE checklist)

Risk of bias – (Chesney et al. [9]) study level (case series) according to IHE [15]	Study/Outcome
Study objective	
1. Was the hypothesis/aim/objective of the study clearly stated?	yes
Study design	
2. Was the study conducted prospectively?	yes

Risk of bias – (Chesney et al. [9]) study level (case series) according to IHE [15]	Study/Outcome
3. Were the cases collected in more than one centre?	yes
4. Were participants recruited consecutively?	yes
Study population	
5. Were the characteristics of the patients included in the study described?	yes
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	yes
7. Did participants enter the study at similar point in the disease?	yes
Intervention and co-intervention	
8. Was the intervention of interest clearly described?	yes
9. Were additional interventions (co-interventions) clearly reported?	yes
Outcome measures	
10. Were relevant outcome measures established a priori?	partial[1]
11. Were outcome assessors blinded to the intervention that patients received?	no[2]
12. Were relevant outcomes appropriately measured with objective and/or subjective methods?	yes
13. Were the relevant outcomes measures made before and after intervention?	yes
Statistical Analysis	
14. Were the statistical tests used to assess the relevant outcomes appropriate?	partial[3]
Results and Conclusions	
15. Was follow-up long enough for important events and outcomes to occur?	partial[4]
16. Were losses to follow-up reported?	yes
17. Did the study provided estimates of the random variability in the data analysis of relevant outcomes?	yes
18. Were the adverse events reported?	yes
19. Were the conclusions of the study supported by results?	yes
Competing interest and source of support	
20. Were both competing interest and source of support for the study reported?	yes

Abbreviations: IHE…Institute of Health Economics

[1] The primary endpoint was measured objectively by an independent review committee (IRC), however, for Cohort 2, the primary endpoint was investigator-assessed and then was changed to IRC-assessed.

[2] Open-label study.

[3] Suitability of pooling Cohort 2 and Cohort 4 is unclear. The authors themselves report that some notable differences were observed in the baseline characteristics between Cohort 2 and 4 and pooling was not pre-specified in the study protocoll.

[4] The duration of response was not reached; long-term data for duration or response, overall survival and objective response rate are missing.

Table 4-4: Statistical analyses in the Chesney et al. study

Study	Statistical analysis
C-144-01 Trial [9]	For Cohort 2, 66 patients were needed to estimate ORR with sufficient precision (two-sided 95% CI width <13.2%) when expecting 20-50% response rates. For Cohort 4, 75 patients were required to test the null hypothesis (ORR ≤10%) against the alternative (ORR >10%) with >90% power, assuming a true response rate of 25%. The primary endpoint analysis employed the Clopper-Pearson exact method for binomial proportions with two-sided confidence limits at an alpha of 0.05. Time-to-event endpoints were analysed using Kaplan-Meier methodology, while safety data was evaluated descriptively.

Abbreviations: CI…confidence interval, ORR…objective response rate

Table 4-5: Evidence profile: Efficacy and safety of the Chesney et al. study [9] based on Grading of Recommendations Assessment, Development and Evaluation (GRADE,[16])

Certainty assessment							Number of participants	Impact	Certainty	Importance
№ of studies	Study design	Risk of biasb	Inconsistency g	Indirectness	Imprecision	Other considerations				
Objective response rate (follow-up: median 27.6 months; assessed with: RECIST V.1.1 IRC-assessed)										
1	NRS[a]	serious[c, d, e, f]	-	not serious	not serious	-ORR of 31,4% in a highly pretreated population with poor prognosis.	153	ORR, n (%) 48 (31.4; 95% CI, 24.1-39.4)	⊕⊕◯◯ low	CRITICAL
Duration of response (follow-up: median 27.6 months; assessed with: RECIST V.1.1 IRC-assessed)										
1	NRS[a]	serious[c, d, e, f]	-	not serious	not serious	The DOR was not evaluable due to the long response during the follow-up.	153	DOR median, months (range), N/R (1.4+ - 45.0+)	⊕⊕◯◯ low	IMPORTANT
Overall survival										
1	NRS[a]	serious[c, d, e, f]	-	not serious	not serious	-	153	OS, median, 13.9 months (95% CI: 10.6-17.8)	⊕◯◯◯ very low	CRITICAL
Progression-free survival										
1	NRS[a]	serious[c, d, e, f]	-	not serious	not serious	-	153	PFS, median, 4.1 months (95% CI: 2.8-4.4)	⊕◯◯◯ very low	IMPORTANT
Grade 3/4 adverse events										
1	NRS[6]	serious[c, d, e, f]	-	not serious	not serious	-	156	Thrombocytopenia 76.9% Anemia 50.0% Febrile neutropenia 41.7 Deaths, n Febrile neutropenia (41.7%)	⊕◯◯◯ very low	IMPORTANT

Abbreviations: CI…confidence interval, DOR…duration of response, IRC…independent review committee, N/R…not reached, NRS…non-randomised studies, ORR…objective response rate, OS…overall survival, PFS…progression-free survival, RECIST…Response Evaluation Criteria in Solid Tumors

Notes:

[a]*As an uncontrolled trial, this study begins with low-certainty evidence due to the lack of randomisation and control group.*

[b] *Moderate methodological quality.*

[c]*The primary endpoint was measured objectively by an independent review committee (IRC), however, for Cohort 2, the primary endpoint was investigator-assessed and then was changed to IRC-assessed.*

[d]*Open-label study.*

[e]*Suitability of pooling Cohort 2 and Cohort 4 is unclear. The authors themselves report that some notable differences were observed in the baseline characteristics between Cohort 2 and 4 and pooling was not pre-specified in the study protocol.*

[f]*The duration of response was not reached, long-term data for duration or response, overall survival and objective response rate are missing.*

[g]*Not applicable, as only one study was graded.*

Table 4-6: Summary table characterising the applicability of the included study

Domain	Description of applicability of evidence
Population	The C-144-01 study included patients with unresectable stage III or stage IV melanoma who progressed after immune checkpoint inhibitors and targeted therapy. The median age was 56.0 years (range, 20-79), with a predominantly male population (54.2%). Most patients had cutaneous melanoma (54.2%), with smaller proportions having mucosal (7.8%) or acral (6.5%) subtypes. Patients had high disease burden at baseline, with a median target lesion sum of diameters of 97.8 mm and elevated LDH levels in 54.2% of cases. The study population was heavily pretreated with a median of 3.0 prior lines of therapy, with 81.7% having received both anti-PD-1 and anti-CTLA-4 therapy, and 54.2% being primary refractory to anti-PD-1/PD-L1 therapy. Notably, this represents a particularly treatment-resistant population with limited therapeutic options.
Intervention	The intervention consisted of a one-time autologous tumour-infiltrating lymphocyte (TIL) cell therapy, lifileucel. The manufacturing process involved resection of tumour (s) from patients, shipment to a centralised good manufacturing practice facility, and a 22-day manufacturing process to produce cryopreserved TIL cells. Patients received a non-myeloablative lymphodepletion regimen (cyclophosphamide and fludarabine) followed by a single lifileucel infusion, then up to six doses of high-dose interleukin-2. The median number of TIL cells infused was 21.1×10^9 (range 1.2×10^9-99.5×10^9). The median time from tumour resection to lifileucel infusion was 33.0 days. No bridging therapy was permitted between tumour resection and lifileucel infusion, which may not reflect real-world clinical practice where bridging therapies might be necessary for patients with rapidly progressing disease. The specialised infrastructure, expertise, and centralised manufacturing process required for lifileucel production may limit its implementation across different healthcare settings, particularly in resource-constrained environments or centres without established cell therapy capabilities.
Comparators	The C-144-01 trial was a single-arm study without active comparators. Historical context suggests limited options after progression on immune checkpoint inhibitors, including cytotoxic chemotherapy (with response rates of 4-12%), ICI rechallenge (response rates ranging from 8-29%), or newer combinations like anti-LAG-3/anti-PD-1 (11.5% response rate). However, the lack of a control arm makes it difficult to establish the relative benefit of lifileucel definitively. Additionally, there was limited information about how standard care varies across different clinical contexts and geographic regions, and no comparisons were made with palliative approaches that might be considered for this heavily pre-treated population. This absence of direct comparators represents a significant limitation in fully contextualising the clinical value of lifileucel relative to other available options for patients with advanced melanoma who have progressed after standard therapies.
Outcomes	The primary endpoint was IRC-assessed objective response rate (ORR), which was 31.4% (95% CI: 24.1% to 39.4%), with 8 complete responses and 40 partial responses. The median duration of response was not reached at a median study follow-up of 27.6 months, with 41.7% of responses maintained for at least 18 months. Median overall survival (OS) was 13.9 months, and median progression-free survival was 4.1 months. In the 5-year analysis of the study, the ORR was 31.4%, the median duration of response was 36.5 months (95% CI: 8.3 to not reached) and 5-year OS rate was 19.7%. The most common grade 3/4 treatment-emergent adverse events were thrombocytopenia (76.9%), anaemia (50.0%), and febrile neutropenia (41.7%). Six deaths occurred within 30 days after infusion, four of which were at-tributed to AEs and two to progressive disease. While the study demonstrated clinical efficacy, long-term durability data beyond the study period remain uncertain, and the study provided limited information on patient-reported outcomes and quality of life.
Setting	The trial was conducted as a multicenter, international Phase 2 clinical trial across multiple sites in the United States and Europe. The centralised manufacturing process requires specialised facilities and expertise, which may limit generalisability to healthcare settings with varying resources. The study did not address differences in healthcare delivery systems across regions, variations in diagnostic criteria and treatment protocols, or the impact of different levels of expertise across centres, which could affect real-world implementation.

Abbreviations: CTLA-4…cytotoxic T-lymphocyte-associated protein 4, ICI…immune checkpoint inhibitor, IRC…independent review committee, LAG-3…lymphocyte activation gene 3, LDH…lactate dehydrogenase, ORR…objective response rate, PD-1…programmed cell death protein 1, PD-L1…programmed death-ligand 1, TIL…tumor-infiltrating lymphocyte

5 Price comparisons, treatment costs and budget impact

5.1 Pharmacoeconomic model(s)

Table 5- 1: Economic evaluation of tumour-infiltating lymphocytes (TIL: product produced in Dutch hospitals)

Author, year [reference]	Country	Intervention and comparator	Target population (base case)	Economic evaluation	Model	Perspective and time horizon	Utility and cost values	Severity modifier	Discount rate	Model assumptions and limitations
Retèl 2018 [19]	NL	Tumour-infiltrating lymphocytes (TIL): surgical resection of metastasis, pre-treatment chemotherapy, after treatment, high-dose bolus interleukin-2 vs ipilimumab (3 mg/kg, every 3 wks, with max. 4 cycles)	Second-line treatment in metastatic melanoma patients	Model-based cost-effectiveness analysis Value of information (VOI) analysis was performed	3 health states: stable disease (responders), progressive disease according to RECIST 1.1. criteria and death; Cycle length: 1 yr	Dutch health care perspective Lifetime horizon (for this population: 10 years)	Utilities: QALYs Costs: measured from the NCI for 10 pts. Including production of TILs, treatment, hospitalisation and management of side effects (estimated €62,000 per patient) Ipilimumab costs based on Dutch official medication prices (estimated €91,487 per patient)	All parameters were varied by +/− 25%, to identify those most influential Discounting by 3,5% for both costs and outcomes Scenario: increased TIL production costs and max. the price that TIL is allowed to have to remain cost-effective	4% for costs and 1.5% for effects	A hypothetical cohort of 1000 patients with metastatic melanoma (stage IV) was simulated, starting at age 52 in the health state "stable disease". Analysis conducted based on the CHEERS guidelines and based on literature (phase II studies) data, e.g. on transition probabilities or probabilities of adverse events. For the VOI analysis: beneficial population 400 pts. per year.

Ten Ham, 2024 [20][5]	NL-NKI; DK-CCIT-DK	Tumour-infiltrating lymphocytes (TIL-NKI/CCIT): surgical resection of metastasis, pre-treatment chemotherapy, after treatment, high-dose bolus interleukin-2, supportive care transfusions vs ipilimumab (3 mg/kg IV, every 3 wks, with max. 4 cycles)	Patients with unresectable stage IIIC–IV melanoma after failure of first-line or second-line treatment	Markov model-based early cost-utility analysis (CUA)	Markov model with 3 mutually exclusive health states: PFS, progressive disease (PD) and death (all causes) Cycle length: 3 mo	Modified societal perspective with a lifetime horizon NL setting as base case, DK setting in a scenario analysis	**Utilities**: QALYs **Costs:** country-specific, Treatment costs for TIL: provided by each center, includes screening, TIL isolation, production, hospital admission and follow-up (€117,940 per patient) Treatment costs for IPI: comprised drug costs, patient hospital admission for treatment and supportive medication (ie, infliximab for adverse events), informed by the Dutch 2021 drug list tariffs (€77,823 per patient) Total costs comprised healthcare resources costs and non-healthcare related costs	**Deterministic sensitivity analyses (DSA):** impact of discounted individual parameters on the ICER by alternately varying input values one by one between pre-set minimum and maximum values, informed by 95% CIs or variance of the mean by ±20%. **Probabilistic sensitivity analyses** (PSA): sampling 10,000 iterations of all model input parameters according to their individual minimum, maximum and distributions, then applying Dutch willingness-to-pay (WTP) of €80,000/incremental QALY. For DK; informal WTP threshold of €50,000/incremental QALY.	In the base case, NL discount rates: 4.0% on costs and 1.5% on benefits (LYs and QALYs) In the DK scenario analysis, 3.5% for both costs and benefits	To extrapolate trial data beyond trial duration to a lifetime horizon, assumptions were made regarding future follow-up activities The optimal time to determine OS of both treatment modalities was not yet reached (statistically insignificant) indirect costs were not collected in line with current HTA-guidelines (the trial was designed under the 2010 Dutch guideline for costing studies)

Abbreviations: CCIT…National Center for Cancer Immune Therapy, CHEERS…Consolidated Health Economic Evaluation Reporting Standards, NCI…Netherlands Cancer Institute, NL…Netherlands, QALY…quality-adjusted life years, RECIST…Response Evaluation Criteria In Solid Tumors, wks…weeks, yr…year

[5] Based on multicenter, open-label randomised phase 3 clinical trial Rohaan et al., 2022 [21].

Table 5- 2: Main results of the included economic evaluations of tumour-infiltating lymphocytes (TIL: lileucel)

Author, year [reference]	Country	Incremental costs (base-case)	Incremental effects (base-case)	ICER (base-case)	CE-threshold applied (base-case)	Sensitivity and scenario analyses	Reflection
Retèl 2018 [19]	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 Expected value of perfect information (EVPI*) amounted to €3 million	TIL 86% probability of being cost-effective at a threshold of €80,000/QALY gained TIL had the highest probability of being cost-effective at 92% certainty at a willingness to pay of €30,000/QALY, remained constant with a 91% certainty at a willingness to pay of €80,000/QALY	Most impact on incremental costs: survival, drop-outs, treatment costs Costs up to € 83,000 per treatment are still below the € 80,000/QALY threshold Most impact on incremental QALYs: survival, utilities TIL would remain less costly, and still be more effective than ipilimumab at costs of up to €77,000 in total (hospitalisation costs stayed equal)	Eligibility criteria: pts. with resectable tumour and no or very limited brain metastases → only 50% of the pts with advanced melanoma are eligible The costs of the TIL production were estimated based on the nonprofit setting of the NCI, If the TIL production were taken over by a (pharmaceutical) company, it is very likely that the (commercial) price would increase considerably
Ten Ham, 2024 [20]	NL and DK	NL base case, undiscounted, lifetime horizon: € 347,168 (TIL) vs € 433,634 (IPI) DK scenario: € 337,309 vs € 436,135	Both NL and DK; undiscounted, lifetime horizon: LYs: 4.47 vs 3.33 QALYs: 3.52 vs 2.46	Dominant ICER (TIL lower total cost than IPI)	**PSA**: The probability of TIL being CE compared to IPI is>99% in both the NL base case (WTP €80,000/QALY) and DK scenario (WTP €50,000/QALY).	**DSA:** Parameters with the most significant impact on ICER: survival probabilities, quality of life in PD and next-line treatment cost in PD	TIL therapy studied in the trial was directly developed by research institutes and hospitals, funded by public money, resulting in lower treatment costs than commercially sourced TIL. Standard of care for patients with melanoma has moved from IPI monotherapy to IPI/nivolumab combination therapy in the course of the trial.

*Abbreviations: LY… life-years; pts: patients, QALYs…quality-adjusted life-years ; *EVPI is the maximum amount the decision maker would be willing to spend to obtain perfect information.*

5.2 Budget impact analysis

Table 5- 3: Estimated population with unresectable or metastatic melanoma and potential candidates for lifileucel in Austria

Population	%	n per year	Reference/assumption
MM incidence Austria, pts.		1960	Austrian incidence data [22]
Stage III	9.0%	176	European average, adapted from [23]
- Stage IIIc	55.0%	97	Assumption based on [24]
○ Stage IIIc, unresectable	4.0%	4	Slovak expert estimations, adapted from [25]
- Stage IIId	3.0%	5	Assumption based on [24]
- Stage IV within the year	23.0%	40	Slovak expert estimations, taken from [25]
Stage IV	7.0%	137	Austrian incidence data [22]
Incident pts. with unresectable and advanced melanoma who shall be treated with PD-L1 each year	SUM	186	
Pts. who need subsequent therapy after PD-L1 treatment	60.0%	112	Assumption based on [26]
BRAF-wild-type (eligible for TIL after progressing on PD-L1)	55.0%	62	Assumption based on [27]
BRAF+ (eligible for BRAF/MEKi after progressing on PD-L1)	45.0%	50	[27]
BRAF+ that will need a subsequent therapy (eligible for TIL after progressing on both PD-L1 and BREF/MEKi)	50.0%	25	[28]
Total assumed number of pts. who will need further treatment (2L for BRAF-WT and 3L for BRAF+)	SUM	87	
Primary scenario: market penetration 20% per year	20.0%	17	The average market penetration of Austrian clinical experts' estimations
Scenario analysis: increasing market penetration over the years (10%, 20%, 30%)	10.0% 20.0% 30.0%	9 18 27	Estimation by Austrian clinical experts

Abbreviations: n...number of patients, pts...patients

Table 5- 4: Unit cost data

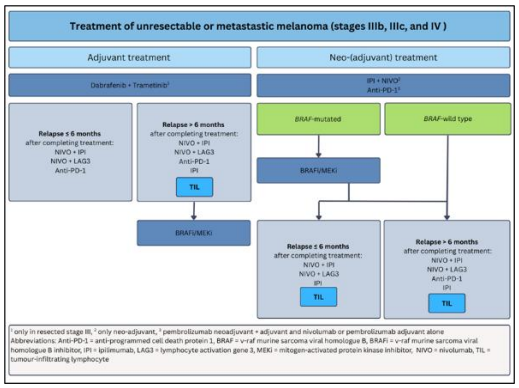
	(Average) unit costs	Range	Reference
A: Lifileucel			
A1: Biopsy of tumour tissue	€300 per intervention	-	LKF data
A2: Inpatient day	€1,571.40 per day	-	LKF-data
A3: ICU day	€3,400 per day	-	LKF-data
A4: Cyclophosphamide (day 1-5)	€1,196 (per administration, code XC232)	-	LKF-data
A5: Fludarabine (day 1-3)	€825 (per administration, code XC552)	-	LKF-data
A6: Interleukin-2	€58 (per administration MEL22.13)	-	LKF-data
A7: Filgrastim (Ratiograstim 30 Mio IE/0.5 ml)	€277.25 per dose	-	EKO-data
B: SoC for previously-treated unresectable or metastatic melanoma			
B1:			
Nivolumab in combination	€1,144 (per administration MEL22.14)	-	LKF-data
wit ipilimumab	€21,250 (per administration MEL22.14)	-	LKF-data
B2:			
Opdualag (nivolumab in combination with relatlimab-rmbw)	€11,530 (per administration MEL22.14)	-	LKF-data

Abbreviations: EKO…Erstattungskodex, LKF…Leistungsorientierte Krankenanstaltenfinanzierung, SoC … standard of care

6 Extended perspectives

6.1 Stakeholder perspectives

Table 6- 1: Questions for clinical experts

<table>
<tr><th colspan="2">Questions about standard of care in Austria</th></tr>
<tr><td>Question 1</td><td>The following treatment algorithm is based on the European Consensus Update 2024. Does this align with the approach in your clinical practice? Especially, regarding the adjuvant treatment (left side)?
 
</td></tr>
<tr><td>Question 2</td><td>What guidelines do you use in your clinical practice? Is it the European consensus, or do you rely on other guidelines (e.g., clinical practice guidelines, country-specific guidelines)?</td></tr>
<tr><td>Questions 3</td><td>Considering the proposed indication: lifileucel for the treatment of adult patients with unresectable or metastatic melanoma (stages IIIb, IIIc and IV) previously treated with a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor, what would be the appropriate comparator treatments in the Austrian clinical setting?</td></tr>
<tr><td>Question 4</td><td>Does the present indication correspond to how lifileucel is intended to be implemented in Austrian clinical practice? Would it be used as the 2L treatment in the BRAF-wild type subpopulation and as the 3L treatment in the BRAF-positive subpopulation (after previous treatment with a PD-1 blocking antibody in 1L, and a BRAF+MEK inhibitor in 2L)?</td></tr>
<tr><td>Question 5</td><td>We found a German registry study from 2019 that presents the distribution of SoC treatment shares after single-agent anti-PD-1 treatment failure, not differentiating for BRAF status. Is this distribution similar in Austria? Can you verify that? How would the distribution change after the introduction of lifileucel in the Austrian market?
<table>
<tr><th>SoC treatment shares after single-agent anti-PD-1 treatment failure and, in case of BRAF-V600 mutation, prior BRAF-/MEK-inhibitor treatment</th><th>Distribution</th><th>Austrian assumption</th><th>Change after lifileucel introduction</th></tr>
<tr><td>ipilimumab and nivolumab</td><td>38,50%</td><td>80%</td><td></td></tr>
<tr><td>ipilimumab monotherapy</td><td>23,50%</td><td></td><td></td></tr>
<tr><td>decarbazin ChT</td><td>16,50%</td><td>-</td><td></td></tr>
<tr><td>BRAF-/MEK inhibitor re-challenge (BRAF-positive patients who underwent BRAF-/MEK-inhibitor treatment prior to anti PD-1 treatment)</td><td>9,00%</td><td>-</td><td></td></tr>
<tr><td>other salvage ChT</td><td>8,50%</td><td>-</td><td></td></tr>
<tr><td>talimogene laherparepvec</td><td>2,00%</td><td>-</td><td></td></tr>
<tr><td>Other, not specified</td><td>2,00%</td><td>-</td><td></td></tr>
<tr><td>Opdualag (nivolumab plus relatlimab-rmbw)</td><td></td><td>20%</td><td></td></tr>
<tr><td>Nivolumab + pembrolizumab</td><td></td><td></td><td></td></tr>
</table></td></tr>
</table>

<table>
<tr><td>Question 6</td><td>Clinically, does it make sense to distinguish patients in the present indication by their BRAF V600 mutation status? If so, how does the treatment differ for patients with a BRAF-V600 mutation? Is BRAF+MEKi re-challenge used in practice?</td></tr>
<tr><td>Question 7</td><td>Apart from the treatment distributions, we require your guidance on the actual treatment durations observed in practice, as the proposed comparators typically specify that treatment should be continued for as long as clinical benefit is observed or until the patient no longer tolerates it.
<table>
<tr><th>Comparator (in 2L+)</th><th>Median treatment duration</th></tr>
<tr><td>Nivolumab + ipilimumab*</td><td>■ 4 cycles?</td></tr>
<tr><td>Opdualag (nivolumab plus relatlimab-rmbw) off-lable</td><td>■ 3 cycles?</td></tr>
<tr><td>Ipilimumab monotherapy</td><td>■ 4 cycles?</td></tr>
<tr><td>Nivolumab monotherapy</td><td>■ ??</td></tr>
<tr><td>Pembrolizumab monotherapy</td><td>■ ??</td></tr>
</table>
*According to the prescription information, the combination phase NIVO+IPI only lasts 4 3-week cycles, but that is followed by NIVO monotherapy phase, which seems to have no prespecified duration (i.e. until effective and tolerated)</td></tr>
<tr><td>Question 8</td><td>What is the role of ChT in the present indication? Is it still used? According to the EU Consensus guideline: … except in specific cases like locoregional tumour-directed chemotherapy, salvage therapy after first-line failure, when inclusion in clinical trials is not possible, or as a temporary measure until other treatments become accessible, traditional cytotoxic chemotherapy should not be considered SoC in the current management of metastatic melanoma.</td></tr>
<tr><td>Question 9</td><td>Are BRAF/MEK inhibitors used as the 2L treatment in all the patients harbouring BRAF V600 mutation (as suggested by the EU consensus-based interdisciplinary guideline for melanoma 2024 update)? Which specific BRAF+MEK inhibitor combinations are used in the 2L, what is their distribution, and what is the median treatment duration?
<table>
<tr><th>BRAF inhibitors
(with MEK inhibitors)</th><th>Used in AT?</th><th>Pts.-Distribution</th><th>Median treatment duration</th></tr>
<tr><td>Dabrafenib
(with Trametinib)</td><td></td><td></td><td></td></tr>
<tr><td>Encorafenib
(with Binimetinib)</td><td></td><td></td><td></td></tr>
<tr><td>Vemurafenib
(with Cobimetinib)</td><td></td><td></td><td></td></tr>
</table></td></tr>
<tr><td colspan="2">Questions about epidemiological data</td></tr>
<tr><td>Question 1</td><td>We tried to derive the maximum eligible population for TIL treatment in Austria. Could you review these numbers and provide more realistic estimates?
<table>
<tr><td>Pts. in stage IV + newly diagnosed pts. in stage IIIc who are eligible for treatment with PD-L1 immunotherapy; regardless of BRAF status</td><td>1497
(prevalence: 1186; incidence: 310)</td><td>Based on prevalence data of AT, SK and CZ and assumptions</td></tr>
<tr><td>of which BRAF-WT (55%)</td><td>823
(prevalence: 653; incidence: 171)</td><td></td></tr>
<tr><td>of these, will need subsequent systemic therapy (48%)</td><td>395
(prevalence: 313; incidence: 82)</td><td>Caroline Robert et al 2020</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>of which BRAF+ (45%)</td><td>674</td><td>EU consensus document</td></tr>
<tr><td>of these, will need subsequent systemic therapy (50%)</td><td>337
(prevalence: 267; incidence: 70)</td><td>Dummer et al., 2022</td></tr>
<tr><td>Overall pts. who need further therapies after 1L (BRAF WT) or 2L (BRAF+)</td><td>732
(prevalence: 580; incidence: 152)</td><td></td></tr>
<tr><td>of these, fit for TIL treatment with subsequent IL-2 administration (considering performance status, renal function, cardiac function, and pulmonary reserve)</td><td>??</td><td>Estimations by clinicians</td></tr>
<tr><td>Estimated market penetration considering the organisational capacities</td><td>50</td><td>Estimations by clinicians</td></tr>
</table></td></tr>
</table>

<table>
<tr><td>Question 2</td><td>Alternatively, we could derive the eligible patient population from the organisational constraints. Which centres would be capable of administering TIL therapy in Austria in the first 3 years after introduction? How many patients could they handle?</td></tr>
<tr><td>Question 3</td><td>What is the expected survival of patients with stage IV melanoma treated with the current standard of care? Is objective response rate of 30% clinically relevant?</td></tr>
<tr><td>Question 4</td><td>Which endpoint is the most relevant one from the patients' perspective from the following: overall survival, progression-free survival, objective response rate, duration of response. Which endpoint would you chose when deciding which therapy to give to the patient?</td></tr>
<tr><td colspan="2">Questions about management of TIL therapy</td></tr>
<tr><td>Question 1</td><td>To check a patient's eligibility for TIL treatment, some studies suggest that the patient undergo specific examinations. Would all these examinations be conducted in practice before lifileucel treatment?
<table>
<tr><th>Physical examinations and tests</th><th>Yes</th></tr>
<tr><td>PET</td><td></td></tr>
<tr><td>CT chest and abdomen</td><td></td></tr>
<tr><td>Lung x-ray photo</td><td></td></tr>
<tr><td>Lung function test</td><td></td></tr>
<tr><td>Brain MRI</td><td></td></tr>
<tr><td>Ejection fraction</td><td></td></tr>
<tr><td>ECG</td><td></td></tr>
<tr><td>Lab tests</td><td></td></tr>
<tr><td>Hematology set</td><td></td></tr>
<tr><td>Chemical set</td><td></td></tr>
<tr><td>Microbiology and oncologic markers set</td><td></td></tr>
<tr><td>Consultations</td><td></td></tr>
<tr><td>Face to face with an advanced practice provider (APP)</td><td></td></tr>
</table></td></tr>
<tr><td>Question 2</td><td>In Expert consensus guidelines on management and best practices for TILL therapy, it is suggested that bridging therapy between the time of surgery and the start of non-myeloablative lymphodepletion should be considered in patients with a high disease burden and patients with rapidly progressive disease or organ impairment that may prevent the patient from receiving TIL cell therapy. Which of these bridging therapies between tumour resection and lymphodepletion would be used in Austria, at what dosage and for how long?
<table>
<tr><th>Bridging therapy between tumour resection and lymphodepletion</th><th>Yes</th><th>Dosage and median duration</th></tr>
<tr><td>BRAF mutation: BRAF/MEK inhibitors</td><td></td><td></td></tr>
<tr><td>BRAF wild-type: single chemotherapy</td><td></td><td></td></tr>
<tr><td>Continuation of immune checkpoint inhibitors (%)</td><td></td><td></td></tr>
<tr><td>Palliative radiation (%)</td><td></td><td></td></tr>
</table></td></tr>
<tr><td>Question 3</td><td>Would the pretreatments with cyclophosphamide (60 mg/kg IV for 2 days) followed by fludarabine (25 mg/m^2 IV for 5 days) be given in the inpatient or outpatient sector?</td></tr>
<tr><td>Question 4</td><td>Are the antibiotics, such as Ceftazidime, Vancomycin, Gentamicin, Streptomycin, and Aminoglycosides cost-relevant?</td></tr>
<tr><td>Question 5</td><td>Filgrastim may be used to manage haematologic toxicities- which one is used in clinical practice at which dose?
<table>
<tr><th>Products</th><th>Yes</th><th>Dosage and median duration</th></tr>
<tr><td>Accofil 12 Mio E/0,2 ml Inj.-/inf.lsg. Fertigspritze 5 St.
Nivestim 12 Mio E/0,2 ml Inj.-/Inf.lsg. 5 St.
Accofil 30 Mio E/0,5 ml Inj.-/Inf.lsg. Fertigspr. 5 St
Nivestim 30 Mio E/0,5 ml Inj.-/Inf.lsg. 5 St.
Ratiograstim 30 Mio IE/0,5 ml mini-Fertigspr. 5 St.
Zarzio 30 Mio E/0,5 ml Inj.-/Inf.lsg. Fertigspr. 5 St.
Accofil 48 Mio E/0,5 ml Inj.-/Inf.lsg. Fertigspr. 5 St.
Nivestim 48 Mio E/0,5 ml Inj.-/Inf.lsg. 5 St.
Ratiograstim 48 Mio IE/0,5 ml mini-Fertigspr. 5 St.
Zarzio 48 Mio E/0,5 ml Inj.-/Inf.lsg. Fertigspr. 5 St.</td><td></td><td></td></tr>
</table></td></tr>
<tr><td>Question 6</td><td>Which interleukin-2 (IL-2) product will be administered to the patient following the TIL infusion? Is it PROLEUKIN (aldesleukin)?</td></tr>
<tr><td colspan="2">Questions about organisational, ethical and social aspects</td></tr>
<tr><td>Question 1</td><td>To our knowledge, there is no dedicated Austrian registry for melanoma, is that correct?</td></tr>
</table>

Question 2	Would it make sense to implement a system like the U.S. TIL Peer Connect"-system (https://www.aimatmelanoma.org/support-resources/connect-with-a-peer/peer-connect-for-til-therapy/) (a peer-to-peer support program matching those who have completed TIL therapy with those undergoing or recovering from it; providing emotional and practical support) in Austria?

Operational considerations for TIL therapy, according to Warner et al. (2023)

Streamlining patient selection and support	Institutional capacity and infrastructure	Surgery	Shipping logistics	Nursing support	Pharmacy support	Cell therapy Lab	Manufacturing	Data/electronic medical record management
Patient education	Training and education of staff	Preferred tumour resection sites and best practices	Precise scheduling	Nurse navigator and nursing staff	Order set creation for non-myeloablative lymphodepleting regimen and IL-2 administration	Possibly TIL manufacturing	Automation, standardization of processes, and environmental control	Defining entities responsible for data platform creation, ensuring accuracy of data collection, logistical challenges of long-term tracking, and funding requirements
Timely referral (coordination betweeen oncologist and surgeon)	Implementing infrastructure requirements	Tumour samples that can be obtained with minimal morbidity	Temperature control	Education programs and trainng	TIL product preparation and infusion	Processing and storage of tumout tissue, process development, lot release testing, and quality control		Establishing electronic medical record workflows
Housing and supportive care considerations	Optimizing processess and workflows		Courier efficiency	Guidelines for dosing, safety mitigation strategies, emergencies, and care escalation	Patient, caregiver, and staff education	Thawing and delivery to bedside		
Social work evaluation	Assess reimbursement strategies				Pharmacovigilance and monitoring			

Abbreviations: IL-2: interleukin 2; TIL: tumour-infiltrating lymphocyte

Figure 6- 1: Operational considerations for TIL cell therapy (adapted from [29])

6.2 Patient's perspective

Table 6- 2: 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	
	48
Indication (self-reported)	
	Malignant melanoma Stage IV
Role	
Patient	2
Carer	0
Member of patient organisation	
Yes	0

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

Table 6- 3: Questions asked to patients with previously treated unresectable or metastatic melanoma

Question 1	Rolle des Ausfüllenden (einzelne/ Patient/Angehörige/Andere)
Question 2	Hauptwohnsitz
Question 3	Mitglied einer Patient:innenorganisation Wenn ja, bitte nennen Sie die Patient:innenorganisation Wenn ja, welche Rolle haben Sie in der Patient:innenorganisation? Wenn ja, welche Erkrankung(en) wird/werden von der Organisation vertreten?
Question 4/1	Krankheitsstadium/ Schweregrad
Question 4/2	Krankheitsgeschichte Wie lange leben Sie schon mit der Krankheit/dem Leiden? Bitte beschreiben Sie Ihre Behandlungsgeschichte
Question 4/3	Zusätzliche Informationen, die Ihrer Meinung nach für die Ersteller des HTA-Berichts hilfreich wären
Question 5	Falls zutreffend, wo haben Sie Informationen über die Erfahrungen der Patient:innen eingeholt? Falls zutreffend, wie haben Sie Informationen über die Erfahrungen der Patient:innen gesammelt?
Question 6	Wie wirkt sich das inoperable oder metastasierte Melanom auf Ihr tägliches Leben (eines Patienten/einer Patientin) aus?
Question 7	Wie wirkt sich das inoperable oder metastasierte Melanom auf Angehörige aus?
Question 8	Wie gut bewältigen Patient:innen mit inoperablem oder metastasiertem Melanom ihre Erkrankung mit den derzeit verfügbaren Therapien?
Question 9	Was erwarten diejenigen Patient:innen, die keine Erfahrung mit Lifileucel (AMTAGVI®) haben, von neuen Therapien im Allgemeinen?
Question 10	Für diejenigen, die Erfahrung mit Lifileucel (AMTAGVI®) haben: Welche Auswirkungen hatte/hat es auf Ihr Leben?
Question 11	Bitte geben Sie alles an, was Ihrer Meinung nach für das für die gemeinsame Bewertung zuständige HTA-Team wissenswert sein könnte.
Question 12	Bitte fassen Sie Ihren Beitrag in maximal zehn Kernaussagen zusammen und listen Sie die wichtigsten Punkte auf.

Abbreviations: HTA…Health Technology Assessment

6.3 Patient's perspective

No additional tables or figures are provided for this subchapter.

6.4 Further ethical and social aspects

No additional tables or figures are provided for this chapter.

7 Development costs and public contributions

Table 7- 1: Financing/patent deals/licensing/funding rounds of all companies involved in the development of Amtagvi®

Type of financing	Details on collaboration, financing, public funding	Year	Amount (in USD)	Funders/ Investors/ Acquiror	Source
Iovance Biotherapeutics (former Lion Biotechnologies, Inc.)					
Post-IPO Equity	Iovance Biotherapeutics, Inc. announces pricing of $211 million underwritten offering of common stock	2024	$211 million	Common stock	https://www.globenewswire.com/news-release/2024/02/20/2831635/0/en/Iovance-Biotherapeutics-Inc-Announces-Pricing-of-211-Million-Underwritten-Offering-of-Common-Stock.html
Acquisition	Iovance Biotherapeutics Inc (NASDAQ: IOVA) has agreed to acquire worldwide rights to Proleukin (aldesleukin), an interleukin-2 (IL-2) product, from Clinigen Limited	2023	£166,7 million (£41,7 million milestone payment)	Clinigen Limited	https://finance.yahoo.com/news/iovance-biotherapeutics-acquires-clinigens-il-163929354.html https://www.sec.gov/Archives/edgar/data/1425205/000155837025006019/iova-20241231xars.pdf
Post-IPO Equity	Iovance Biotherapeutics Announces Pricing of its Public Offering Of $150 Million of Common Stock	2023	$150 million	Public offering of common stock	https://www.reuters.com/article/business/healthcare-pharmaceuticals/iovance-biotherapeutics-announces-pricing-of-its-public-offering-of-150-million-idUSASB0C2BS/
Post-IPO Equity	DLA Piper advises Iovance Biotherapeutics in its US$604 million common stock offering	2020	$603,7 million	Public offering of common stock	https://www.biospace.com/dla-piper-advises-iovance-biotherapeutics-in-its-us-604-million-common-stock-offering
Post-IPO Equity	Iovance Biotherapeutics, Inc. announces closing of $252 million common stock public offering	2018	$252,2 million	Public offering of common stock	https://www.sec.gov/Archives/edgar/data/1425205/000114420418054098/tv504904_ex99-1.htm
Post-IPO Equity	Iovance biotherapeutics, Inc. announces closing of $172.5 million common stock public offering	2018	$172,5 million	Public offering of common stock	https://www.globenewswire.com/en/news-release/2018/01/29/1313877/0/en/Iovance-Biotherapeutics-Inc-Announces-Closing-of-172-5-Million-Common-Stock-Public-Offering.html

Type of financing	Details on collaboration, financing, public funding	Year	Amount (in USD)	Funders/ Investors/ Acquiror	Source
Strategic Alliance Agreement	Iovance Biotherapeutics, Inc. provides a total funding of $14.2 million for clinical and preclinical research studies and all related IP of inventions go to Iovance Biotherapeutics	2017-2024 (but extended)	$14,2 million	Research funding	https://www.sec.gov/Archives/edgar/data/1425205/000155837025006019/iova-20241231xars.pdf
Post-IPO Equity	Lion Biotechnologies raises approximately $100 million in private placement	2016	$100 million	Private placement	https://www.reuters.com/article/business/healthcare-pharmaceuticals/lion-biotechnologies-raises-about-100-mln-in-private-placement-idUSASC08SLK/
Post-IPO Equity	Lion Biotechnologies, Inc. (Nasdaq:LBIO), a biotechnology company that is developing novel cancer immunotherapies based on tumor infiltrating lymphocytes (TIL), today announced the pricing of an underwritten public offering of 8,000,000 shares of its common stock at a public offering price of $8.00 per share. The gross proceeds from this offering to Lion are expected to be $64.0 million, before deducting underwriting discounts and commissions and offering expenses payable by Lion.	2015	$64,0 million	Public stock offering	https://www.biospace.com/lion-biotechnologies-inc-prices-public-offering-of-common-stock
Private financing	Lion Biotechnologies, Inc. Eyes Approximately $23 Million in Private Financing	2013	$23 million	Venture capital	https://www.biospace.com/lion-biotechnologies-inc-eyes-approximately-23-million-in-private-financing
Genesis Biopharma (formerly Freight Management Corp)					
Merger	Genesis Biopharma, Inc. Announces Completion of Merger with Lion Biotechnologies	2013	n.a.	Lion Biotechnologies (Iovance Biotherapeutics)	https://www.biospace.com/genesis-biopharma-inc-announces-completion-of-merger-with-b-lion-biotechnologies-b
Post-IPO Equity	Genesis Biopharma, Inc. places its equity for funding	2013	$1,35 million	Not disclosed	https://www.sec.gov/Archives/edgar/data/1425205/000151316013000035/xslFormDX01/primary_doc.xml
Post-IPO Debt	Genesis Biopharma, Inc. takes on debt from 5 non-disclosed debtors	2011	$5 million	Not disclosed	https://www.sec.gov/Archives/edgar/data/1425205/000114420411044671/xslFormDX01/primary_doc.xml

Type of financing	Details on collaboration, financing, public funding	Year	Amount (in USD)	Funders/ Investors/ Acquiror	Source
Venture - Series Unknown	Genesis Biopharma, Inc. places its equity for funding	2011	$640.000	Venture capital funding	https://www.sec.gov/Archives/edgar/data/1425205/000148380611000003/xslFormDX01/primary_doc.xml
Origins in general	Dr. Steven Rosenberg, Chief of the Surgery Branch at the National Cancer Institute, developed a process whereby TILs are isolated directly from the patient's tumor, multiplied to great numbers, and infused into the patient to destroy the patient's cancer. Contego™ is based on the TIL therapy developed by Dr. Rosenberg for the treatment of patients with Stage IV metastatic melanoma.	2012	n.a.	National Cancer Institute	https://www.fiercepharma.com/pharma/base-technology-for-genesis-biopharma-s-contego-tm-featured-cnn-report-md-anderson-s
Private Financing	Genesis Biopharma Announces $700K Private Financing	2010	$700.000	n.a.	https://www.fiercebiotech.com/biotech/genesis-biopharma-announces-700k-private-financing
VC	Combination of equity and warrants for funding	2010	$ 500.000	Venture capital	http://www.sec.gov/Archives/edgar/data/1425205/000148380610000005/xslFormDX01/primary_doc.xml
Seed	Equity offering	2010	$ 250.000	One non-disclosed investor	http://www.sec.gov/Archives/edgar/data/1425205/000148380610000007/xslFormDX01/primary_doc.xml
National Cancer Institute					
Basic research	Adoptive Cell Transfer Immunotherapy of Cancer (PI Steven Rosenberg)	2008-2024	$53.785.735	National Cancer Institute	https://reporter.nih.gov/search/W9vFhITe502y9n3FdEATRQ/projects
Early basic research (proof of concept)	The Immunotherapy of Animal and Human Cancer (PI Steven Rosenberg)	1999-2007	$3.172.648 (only data for 2007 is available)	National Cancer Institute	https://reporter.nih.gov/search/eWdeLcwr6U-8QValczkQMQ/projects
University Of Tx Md Anderson Can Ctr					
Basic research	Functional Attributes of a CD8+BTLA+ T cell subset in Adoptive T Cell Therapy (PI Chantale Bernatchez)	2013-2014	$376.536	National Cancer Institute	https://reporter.nih.gov/search/AJFF9ihLnkivZP8I6wcXIQ/project-details/8681400

Type of financing	Details on collaboration, financing, public funding	Year	Amount (in USD)	Funders/ Investors/ Acquiror	Source
	Biology Of Human Tumor Infiltrating Lymphocytes	1989-1991	$138.671 $138.002 $139.389	National Cancer Institute	https://reporter.nih.gov/search/4oyR-zdv-kqxiOUq-ZO-Nw/project-details/3191720 https://reporter.nih.gov/search/4oyR-zdv-kqxiOUq-ZO-Nw/project-details/3191718 https://reporter.nih.gov/search/4oyR-zdv-kqxiOUq-ZO-Nw/project-details/3191719
H. Lee Moffitt Cancer Center & Research Institute					
Basic research	Co-Stimulation to Enhance Adoptive Cell Therapy for Metastatic Melanoma (PI Amod Sarnaik)	2013-2017	$826.070	National Cancer Institute	https://reporter.nih.gov/search/I7Ky5CPduE6yED0G0Wy-eQ/projects
Basic research	PD-1 Abrogation and Immunity in Melanoma	2009-2013	$1.591.223	National Cancer Institute	https://reporter.nih.gov/search/cq9SGBDPyEWs2JRMmg71jg/project-details/7766967
Basic research	Rational Sequencing of PD-1 and CTLA-4 Antibodies in Metastatic Melanoma	2013-2017	$1.671.227	National Cancer Institute	https://reporter.nih.gov/search/cq9SGBDPyEWs2JRMmg71jg/project-details/8483472
Basic research	Anti-melanoma Activity of Combined Lymphopenia and Immunotherapy	2008-2012	$945.241	National Cancer Institute	https://reporter.nih.gov/search/Tg_mjQqd5U6KeyUs7LV1YQ/project-details/8114435
Capacity building	Leveraging the Lymphocytic Infiltration of Soft Tissue Sarcoma for Autologous Cellular Immunotherapy	2020-2024	$1.226.480	National Cancer Institute	https://reporter.nih.gov/search/PGu_9TEZkEODx1TW_cOf8A/project-details/10038950
Yale University					
Basic research in improving efficacy for future research	Enhancing Melanoma TIL Efficacy with Multifactor mRNA-Mediated T Cell Reprogramming	2023-2024	$538.582	National Cancer Institute	https://reporter.nih.gov/search/82BWIrX6UEGkjXG7RyApFw/project-details/10721549
Basic research	Enhancement Of Anti-Tumor Immunity By Inhibition Of Tgf-B Signaling In Patiens Wi	2006-2010	$140.694 $256.461 $256.461 $256.461 $256.461	National Cancer Institute	https://reporter.nih.gov/search/SYAaU5kAA0qwlviNzvM1iQ/project-details/7147300 https://reporter.nih.gov/search/SYAaU5kAA0qwlviNzvM1iQ/project-details/7454466 https://reporter.nih.gov/search/SYAaU5kAA0qwlviNzvM1iQ/project-details/7664622 https://reporter.nih.gov/search/SYAaU5kAA0qwlviNzvM1iQ/project-details/7901165

Type of financing	Details on collaboration, financing, public funding	Year	Amount (in USD)	Funders/ Investors/ Acquiror	Source
					https://reporter.nih.gov/search/SYAaU5kAA0qwlviNzvM1iQ/project-details/8104129
Basic research	Project 4-Modulating Innate Immunity to Overcome Resistance to PD-1/PD-L1 Blockade	2018-2022	$1.664.749	National Cancer Institute	https://reporter.nih.gov/search/6yr5fXP97kaz16yOkowqJg/projects
Proof-of-concept	Programmed Cell Death 1 + Selected Cell Therapy With Durvalumab (MEDI4736) and Tremelimumab in Metastatic Melanoma	2020-2025	n.a.	AstraZeneca (collaborator)	https://clinicaltrials.gov/study/NCT04223648
University Of Southern California					
Basic research	CTLA-4 Inhibition and Autoimmunity in Melanoma	2004-2008	$2.420.224	National Cancer Institute	https://reporter.nih.gov/search/cq9SGBDPyEWs2JRMmg71jg/project-details/7121054
University Of Pittsburgh At Pittsburgh					
Basic research	Melanoma Program (Project-008)	2015-2021	$185.537	National Cancer Institute	https://reporter.nih.gov/search/V8SNmLIhoE2-nUHOuRsQ7g/projects
Basic research	SPORE in Skin Cancer	2008-2024	$22.894.338	National Cancer Institute	https://reporter.nih.gov/search/erqZzZ3uU0yZNzrMUpDtzA/projects?sort_field=fiscal_year&sort_order=desc
Basic research	Metabolic Reprogramming of Tumor Infiltrating Lymphocytes for Adoptive Immunotherapy	2019-2023	$1.775.650	National Cancer Institute	https://reporter.nih.gov/search/QyB-p8nv9Uy2oJzeOsmMpg/project-details/10636878
Fred Hutchinson Cancer Research Center					
Basic research	Therapy Of Melanoma With Antigen-Specific T Cell Clones	1996-2002	$838.780 $559.784	National Cancer Institute	https://reporter.nih.gov/search/1gs96aSF1kydYnJPZmjI_Q/project-details/2115374 https://reporter.nih.gov/search/1gs96aSF1kydYnJPZmjI_Q/project-details/6339917
University of Chicago					
Basic research	Tumor Recognition by TCR Transduced CD4+ and CD8+T Cells	2001-2004	$1.253.300	National Cancer Institute	https://reporter.nih.gov/search/GgILY87_Jk6uCsgKgAB09g/project-details/6320490
Loyola University Chicago					
Basic research	TCR Transduced CD4+ T Cells for Adoptive Immunotherapy	2012	$269.531	National Cancer Institute	https://reporter.nih.gov/search/iH7QKeOZbka1pLN2P6lD4w/project-details/8555358
Basic research	TCR Transduced CD4 T Cells for Adoptive Immunotherapy	2015	$216.049	National Cancer Institute	https://reporter.nih.gov/search/iH7QKeOZbka1pLN2P6lD4w/project-details/8929164
Basic research	TCR Gene Modified T Cells for Adoptive Immunotherapy	2011-2015	$15.369.075	National Cancer Institute	https://reporter.nih.gov/search/iH7QKeOZbka1pLN2P6lD4w/project-details/8929161
The Christie NHS Foundation Trust					

Type of financing	Details on collaboration, financing, public funding	Year	Amount (in USD)	Funders/ Investors/ Acquiror	Source
Basic research	TIL Therapy in Metastatic Melanoma and IL2 Dose Assessment (METILDA)	2014-2015	n.a.	The Christie NHS Foundation Trust National Institute for Health Research	https://clinicaltrials.gov/study/NCT01995344#more-information
The Netherlands Cancer Institute					
Late-stage clinical development	Study Comparing TIL to Standard Ipilimumab in Patients With Metastatic Melanoma (TIL)	2014-2023	n.a.	The Netherlands Cancer Institute Copenhagen University Hospital at Herlev Dutch Cancer Society	https://clinicaltrials.gov/study/NCT02278887#collaborators-and-investigators https://clinicaltrial.be/en/details/11551?per_page=20&only_recruiting=0&only_eligible=0&only_active=0
	Collaboration project with Herlev hospital to improve TIL technology for seriously ill melanoma patients	2020-2022	4.3 million DKK (Danish krone)	Collaboration between Herlev hospital and CBio A/S	https://innovationsfonden.dk/en/investments/investments-overview?field_program_target_id=&field_start_year_value=&field_area_target_id=All&search=Herlev
	Behandeling van uitgezaaid melanoom met T cel therapie na falen op anti-PD1, hoe kunnen we de gerandomiseerde studie afronden?	2019-	n.a.	The Netherlands Cancer Institute	https://www.kwf.nl/onderzoek/onderzoeksdatabase/behandeling-van-uitgezaaid-melanoom-met-t-cel-therapie-na-falen-op
TRAMPOLINE PHARMA, INC.					
Capacity building	Next Generation Autologous TIL Cancer Therapy: Development of GMP manufacturing process	2022-2023	$2.000.000	National Cancer Institute	https://reporter.nih.gov/search/QyB-p8nv9Uy2oJzeOsmMpg/project-details/10685604
Leiden University					
Basic research	TIL and Anti-PD1 in Metastatic Melanoma (ACTME)	2018-2025	n.a.	Leiden University Bristol-Myers Squibb	https://clinicaltrials.gov/study/NCT03638375#collaborators-and-investigators
Institut Claudius Regaud					
Translational proof-of-concept	Evaluation of Sphingolipids as Predictive Biomarkers of Immune Checkpoint Inhibitor Response in Melanoma Patients (IMMUSPHINX)	2019-2024	n.a.	Nantes University Hospital (collaborator)	https://clinicaltrials.gov/study/NCT03627026
TILT Biotherapeutics Ltd.					
Basic and applied research	TNFalpha and Interleukin 2 Coding Oncolytic Adenovirus TILT-123 During TIL Treatment of Advanced Melanoma (TUNINTIL)	2020-2024	n.a.	Copenhagen University (collaborator)	https://clinicaltrials.gov/study/NCT04217473

Type of financing	Details on collaboration, financing, public funding	Year	Amount (in USD)	Funders/ Investors/ Acquiror	Source
				Nantes University Hospital (collaborator)	

Abbreviations: BTLA+...B and T Lymphocyte Attenuator positive, CD4+...Cluster of Differentiation 4 positive, CD8+...Cluster of Differentiation 8 positive, Corp...Corporation, CTLA-4...Cytotoxic T-Lymphocyte Associated Protein 4, DKK...Danish Krone, GMP...Good Manufacturing Practice, IL-2...Interleukin-2 ,Inc....Incorporated, IP...Intellectual Property, IPO...Initial Public Offering, Ltd....Limited, mRNA...messenger Ribonucleic Acid, n.a....not available, NHS...National Health Service, PD-1...Programmed Cell Death 1, PD-L1...Programmed Cell Death Ligand 1, PI...Principal Investigator, TCR...T-Cell Receptor, TGF-β...Transforming Growth Factor beta, TIL...Tumor Infiltrating Lymphocytes, USD...United States Dollar VC...Venture Capital

Table 7- 2: Search terms used to identify the development history and public contributions of AMTAGVI®

Database/ News outlet/ clinical trial registry/ funding website	Search terms used	Additional search terms	Relevant information found (Yes/no)	Search period	Type of information extracted
https://www.ema.europa.eu/en/medicines	Lifileucel Amtagvi IL-2	n.a.	No	Earliest mention – 05/2025	Active substance, Medical specialty, Pharmacotherapeutic group, Therapeutic area, Class, Orphan designation, Categorization, Additional monitoring, Conditional approval, Accelerated assessment, PRIME: priority medicines, Marketing authorization issued
https://adisinsight.springer.com/			Yes		Alternative names
https://pubmed.ncbi.nlm.nih.gov/	Lifileucel Amtagvi IL-2 Autologous TILs LN-144 Tumour infiltrating lymphocytes 2306267-74-1 r0835e18nh		Yes		Development history
https://clinicaltrials.gov/			Yes		Clinical trials
https://euclinicaltrials.eu/			Yes		
https://eudract.ema.europa.eu/			Yes		
https://trialsearch.who.int/			Yes		
https://cordis.europa.eu/			Yes		
https://reporter.nih.gov/		Steven Rosenberg Marie-Andrée Forget Rodabe N. Amaria James Isaacs M.D. Anderson Cancer Center Orlando Memorial Sloan-Kettering Cancer Center H. Lee Moffitt Cancer Center And Research Jason A Chesney Amod A Sarnaik	Yes		Basic research. Authors selected based on literature found on PubMed
https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm			No		Patent information and associated references
https://competition-cases.ec.europa.eu/search			No		Funding amounts
https://www.ihi.europa.eu/			No		
https://eismea.ec.europa.eu/index_en			No		
https://eit.europa.eu/			No		
https://eic.ec.europa.eu/index_en			No		

https://www.eib.org/en/index		Omid Hamid	No		
https://research-and-innovation.ec.europa.eu/funding/funding-opportunities/funding-programmes-and-open-calls_en		Karl D Lewis Nikhil I Khushalani Theresa Medina Harriet M Kluger	No		
https://www.sbir.gov/		Sajeve S Thomas	Yes		Project funding for companies involved in the development
https://www.nsf.gov/		Evidio Domingo-Musibay	Yes		SME, national, regional, local, international, supranational funding
https://www.ukri.org/		Anna C Pavlick	No		
https://foerderportal.bund.de/		Eric D Whitman	No		
https://www.health-holland.com/		Pippa Corrie	Yes		
https://www.bpifrance.com/		Brendan D Curti	Yes		
https://www.inserm.fr/en/home/		Judit Oláh	No		
https://innovationsfonden.dk/da		Jose Lutzky	yes		
https://lundbeckfonden.com/en		Jeffrey S Weber			
https://www.ucc.ie/en/apc/		Madan Jagasia	No		
https://www.amractionfund.com/about		Toshimi Takamura	No		
https://www.gatesfoundation.org/		Wen Shi	No		
		Harry Qin Xiao Wu			
https://www.google.com/		Cecile Chartier	Yes		Patent information
https://www.forbes.com/		Friedrich Graf Finck-enstein	No		n.a.
https://www.reuters.com/			Yes		
https://www.science.org/		Maria Fardis	No		
https://www.cafepharma.com/		Jason A Chesney	No		Collaborations, funding, financing, patent disputes, acquisitions
https://www.livescience.com/			No		
https://www.biospace.com/			No		
https://www.bioworld.com/			No		
https://www.biopharmadive.com/			No		
https://pharmaphorum.com/			No		
https://pharmatimes.com/			No		
https://pharmafile.com/			No		
https://www.fiercepharma.com/			No		
https://www.businesswire.com/			No		
https://www.businessinsider.com/			No		
https://www.statnews.com/			No		
https://finance.yahoo.com			Yes		

https://www.globenewswire.com			Yes		
https://www.sec.gov/			Yes		

8 Landscape overview

8.1 Ongoing studies on lifileucel

Table 8- 1: List of ongoing studies with lifileucel [30]

Title	Trial ID	Other IDs	Phase	Status	Estimated study completion date	Additional information
Expanded Access Program of AMTAGVI That is Out of Specification for Commercial Release	NCT05398640	IOV-EAP 402	Expanded Access	-	-	The objective is to provide access to Out Of Specification AMTAGVI treatment to patients.
Study to Investigate Lifileucel Regimen Plus Pembrolizumab Compared With Pembrolizumab Alone in Participants With Untreated Advanced Melanoma.	NCT05727904	IOV-MEL-301	Phase 3	Recruiting	2028-03-01	Objective is to assess the efficacy and safety of lifileucel in combination with pembrolizumab compared with pembrolizumab alone in participants with untreated, unresectable or metastatic melanoma.
Lifileucel With Reduced Dose Fludarabine/Cyclophosphamide Lymphodepletion and Interleukin-2 for the Treatment of Patients With Unresectable or Metastatic Melanoma	NCT06151847	STUDY00150697	Phase 2	Recruiting	2025-11-27	The trial tests how well lifileucel, with reduce dose fludarabine and cyclophosphamide for lymphodepletion and interleukin-2, work for treating patients with melanoma that cannot be removed by surgery (unresectable) or that has spread from where it first started (primary site) to other places in the body (metastatic)
Study of Autologous Tumor Infiltrating Lymphocytes in Patients With Solid Tumors	NCT03645928	IOV-COM-202	Phase 2	Recruiting	2029-08-09	Evaluation of adoptive cell therapy with lifileucel in combination with immune checkpoint inhibitors or lifileucel and LN-145-S1 as a single agent therapy.

8.2 Treatments in development

Table 8- 2: Landscape overview for unresectable second-line or later therapies

Indication	Active ingredient	NCT Number	Originator	Developer	Estimated EC decision
RAPA-201					
RAPA-201 monotherapy for second line treatment of metastatic unresectable Melanoma in adults and elderly	Rapa-201	NCT06708455	n.a.	Rapa Therapeutics	Jul 2029
[212pb]vmt01					
[212pb]vmt01 in combination with nivolumab or as monotherapy for second line or later treatment of unresectable or metastatic MC1R positive Melanoma in adults and elderly	[212pb]vmt01	NCT05655312	n.a.	Perspective Therapeutics	Unknown
IBI363					
Ibi363 monotherapy for second line or later treatment of unresectable, locally advanced or metastatic Melanoma in adults and elderly	Ibi363	NCT06281678 NCT06081920	n.a.	Innovent Biologics	Unknown
Alrizomadlin					
Alrizomadlin monotherapy for second line treatment of relapsed/refractory, metastatic or unresectable Melanoma in adults and elderly after PD-1/PD-L1 treatment	Alrizomadlin	NCT03611868	n.a.	Ascentage Pharma	Unknown
Imm-1-104					
Imm-1-104 monotherapy for second line or later treatment of metastatic or locally advanced unresectable, RAS-mutant Melanoma in adults and elderly	Imm-1-104	NCT05585320	n.a.	Immuneering	May 2030
Iov-3001					
Iov-3001 monotherapy for second line or later treatment of unresectable or metastatic Melanoma in adults and elderly who will receive lifileucel	Iov-3001	NCT06940739	n.a.	Iovance Biotherapeutics	Unknown
Bi-1607					
Bi-1607 in combination with pembrolizumab and ipilimumab for second line or later treatment of unresectable or metastatic Melanoma in adults and elderly	Bi-1607	NCT06784648	n.a.	BioInvent	Unknown
Igrelimogene litadenorepvec					
Igrelimogene litadenorepvec in combination with lymphocyte-depleting chemotherapy and TILs for second line or later treatment of refractory or recurrent stage 3-4, metastatic Melanoma in adults and elderly	Igrelimogene Litadenorepvec	NCT0421747 NCT06961786	n.a.	TILT Biotherapeutics	Oct 2030

Indication	Active ingredient	NCT Number	Originator	Developer	Estimated EC decision
LN-145-S1					
Ln-145-s1 monotherapy for second line treatment of metastatic stage IIIC to IV unresectable Melanoma in adolescents, adults and elderly who previously received systemic therapy with a PD-1 blocking antibody	Ln-145-s1	NCT03645928	n.a.	Iovance Biotherapeutics	Unknown
Lucicebtide					
Lucicebtide monotherapy for second line or later treatment of locally advanced or metastatic unresectable Melanoma in adults and elderly who have progressed after/or on treatment with an immune checkpoint inhibitor (CPI)	Lucicebtide	NCT04478279	n.a.	Sapience Therapeutics	Unknown
Naporafenib					
Naporafenib in combination with trametinib for second line treatment of metastatic or unresectable NRAS mutation-positive Cutaneous melanoma in adults and elderly who progressed on or are intolerant to a PD-1/PD-L1–based regimen	Naporafenib	NCT02974725 NCT04417621 NCT06346067	n.a.	Erasca	Aug 2029
Tucidinostat					
Tucidinostat in combination with nivolumab for first line or later treatment of metastatic or unresectable non-uveal Melanoma in adolescents, adults and elderly who were not previously treated with PD-1 or PD-L1 inhibitors	Tucidinostat	NCT04674683	n.a.	HUYA Bioscience International	Oct 2026
LNS8801					
LNS8801 monotherapy for second line or later treatment of refractory, metastatic and/or unresectable Cutaneous melanoma in adults and elderly who are homozygous for the consensus GPER protein-coding amino acid sequence and have progressed on an anti-PD-1 therapy	Lns8801	NCT06624644	n.a.	Linnaeus Therapeutics	Dec 2029
IMA203					
IMA203 in combination with adjuvant low dose interleukin (IL)-2 for second line or later treatment of metastatic or unresectable HLA-A*02:01-positive Cutaneous melanoma in adults and elderly with disease progression on or after at least one PD-1 inhibitor	Ima203	NCT03686124 NCT06743126	n.a.	Immatics	Apr 2028
Rose Bengal Sodium					
Rose bengal sodium in combination with pembrolizumab for first line or later treatment of unresectable, in-transit, or satellite stage III or IV Malignant melanoma in adults and elderly	Rose Bengal Sodium	NCT02557321 NCT00521053 NCT02288897	n.a.	Provectus Biopharmaceuticals	Unknown
KIMMTRAK®					

Indication	Active ingredient	NCT Number	Originator	Developer	Estimated EC decision
Tebentafusp in combination with pembrolizumab for second line or later treatment of stage III or IV unresectable HLA-A*02:01 positive non-ocular Melanoma in adults and elderly who have progressed on an anti-PD1, received prior ipilimumab and, if applicable, received a BRAF kinase inhibitor	Tebentafusp	NCT05549297	n.a.	Immunocore	Oct 2027
Vusolimogene oderparepvec					
Vusolimogene oderparepvec in combination with nivolumab for second line treatment of advanced cutaneous melanoma in adolescents, adults and elderly who progressed on anti-PD-1 and anti-CTLA-4 containing treatment or are ineligible for anti-CTLA-4 treatment	Vusolimoegene oderparepvec	NCT03767348	n.a.	Replimune	Jul 2026

8.3 Published studies on other TIL products

Table 8- 3: Characteristics of included studies to other TIL therapies produced in hospitals

Reference/ ID	Forget et al. 2018 [31]	Khammari et al. 2020 [32]	Rohaan et al. 2022 [21]	Fradley et al. 2022 [33]
Study type and design (NCT)	Phase 2, open-label study (NCT00338377)	Phase 3, open-label, randomised two-arm, multicenter study (NCT00200577)	Phase 3, multicenter, open-label study (NCT02278887)	Retrospective safety study at a single center.
Place of TIL production	The University of Texas MD Anderson Cancer Center, USA	University Hospital of Nantes, France	Netherlands Cancer Institute, Amsterdam National Center for Cancer Immune Therapy, Copenhagen	Moffitt Cancer Center, USA
Study population	Patients ≥12 years of age with locally advanced stage III or stage IV melanoma.	Patients ≥18 years of age with stage III melanoma with only one invaded lymph node.	Patients ≥18 years of age with unresectable stage IIIC or stage IV melanoma.	All patients who received ACT-TIL treatment for melanoma as part of 1 of 3 investigator initiator trials at the Moffitt Cancer Center between 2010 and 2016.
Study arm(s)	TIL (N=74)	TIL (N=26) Abstention (N=23)	TIL (N=84) Ipilimumab (N=84)	TIL (N=43)

Reference/ ID	Forget et al. 2018 [31]	Khammari et al. 2020 [32]	Rohaan et al. 2022 [21]	Fradley et al. 2022 [33]
Follow-up data, cut-off (s) and locations	Median follow-up: 74 months Treated between: 08/2007-05/2015 Locations: University of Texas MD Anderson Cancer Center	Follow-up: 60 months Study duration: 06/2005-01/2013 Locations: CHU Nantes (University Hospital of Nantes), CHU A Michallon in Grenoble, CHU de Montpellier (University Hospital of Montpellier)	Median follow-up: 33 months Completion date: 12/2023 Data cut off: 06/2022 Locations: The Netherlands Cancer Institute (Amsterdam, Netherlands), The National Center for Cancer Immune Therapy, Copenhagen University Hospital (Herlev, Denmark)	Mean follow-up: 32 months Study duration: 2010-2016 Locations: Moffitt Cancer Center, USA
Study endpoints (primary and secondary)	Endpoints: BOR, OS, PFS	Primary endpoint: DFS Secondary endpoints: OS[a]	Primary endpoint: PFS (RECIST v1.1) Secondary endpoints: PFS (immune-related response criteria), OR, OS, HRQoL	Cardiovascular events
Dosing of TIL	Freshly harvested and washed autologous TIL administered intravenously on day 0.	Intravenous administration of cryopreserved TIL of dose 3.6 × 10^9 to 17.4 × 10^9.	Single intravenous administration of TIL of dose 5×10^9 to 2×10^{11}.	TIL administered intravenously on day 0.
Dosing of IL-2	720,000 IU/kg on day 1 every 8 hours to tolerance for a maximum of 15 doses.	6 000 000 IU between day 1 and day 5 and between day 8 and day 12.	600,000 IU/kg per dose every 8 hours, for a maximum of 15 doses per protocol.	720,000 IU/kg up to 15 doses every 8 hours.
Lymphodepleting procedure	Cyclophosphamide 60 mg/kg per day for 2 days intravenously and fludarabine 25 mg/m^2 per day for 5 days intravenously prior to TIL.	None.	Cyclophosphamide 60 mg/kg per day for 2 days intravenously and fludarabine 25 mg/m^2 per day for 5 days intravenously prior to TIL.	Cyclophosphamide 60 mg/kg per day for 2 days intravenously and fludarabine 25 mg/m^2 per day for 5 days intravenously prior to TIL.
Dosing of comparator	-	-	3 mg of ipilimumab/kg intravenously every 3 weeks, for a maximum of 4 doses.	-

Abbreviations: ACT…adoptive cellular therapy, BOR…best overall response, DFS…disease-free survival, HRQoL…health-related quality of life, IL…interleukin-2, N…number of participants, OR…objective response, OS…overall survival, PFS…progression-free survival, RECIST…Response Evaluation Criteria in Solid Tumors, TIL…tumor-infiltrating lymphocyte therapy, USA…United States of America

Notes: [a]for other endpoints, see the reference

9 Discussion

No additional tables or figures are provided for this chapter.

10 References

[1] Strashilov S. and Yordanov A. Aetiology and Pathogenesis of Cutaneous Melanoma: Current Concepts and Advances. Int J Mol Sci. 2021;22(12). Epub 20210615. DOI: 10.3390/ijms22126395.

[2] Curiel-Lewandrowski C. Melanoma: Epidemiology and risk factors. 2025 [cited 29.04.2025]. Available from: https://www.uptodate.com/contents/melanoma-epidemiology-and-risk-factors?search=melanoma&topicRef=4843&source=see_link.

[3] National Cancer Institute (NCI). PDQ® Adult Treatment Editorial Board. Melanoma Treatment (PDQ®)–Patient Version. 2025 [cited 29.04.2025]. Available from: https://www.cancer.gov/types/skin/patient/melanoma-treatment-pdq.

[4] Garbe C., Amaral T., Peris K., Hauschild A., Arenberger P., Basset-Seguin N., et al. European consensus-based interdisciplinary guideline for melanoma. Part 1: Diagnostics - Update 2024. European Journal of Cancer. 2025;215:115152. Epub 20241128. DOI: 10.1016/j.ejca.2024.115152.

[5] Swetter S. G., Alan C. Melanoma: Clinical features and diagnosis. 2023 [cited 29.04.2025]. Available from: https://www.uptodate.com/contents/melanoma-clinical-features-and-diagnosis?search=melanoma&source=search_result&selectedTitle=1%7E150&usage_type=default&display_rank=1#H81531020.

[6] Ward J. P. Tumor Infiltrating Lymphocytes (TIL): From Bench to Bedside. 2022. p. 223-248.

[7] Pschyrembel Online. MEK-Kinase-Inhibitoren. 2019 [cited 12.05.2025]. Available from: https://www.pschyrembel.de/MEK-Kinase-Inhibitoren/Z043X.

[8] Personal Communication with clinical experts.

[9] Chesney J., Lewis K. D., Kluger H., Hamid O., Whitman E., Thomas S., et al. Efficacy and safety of lifileucel, a one-time autologous tumor-infiltrating lymphocyte (TIL) cell therapy, in patients with advanced melanoma after progression on immune checkpoint inhibitors and targeted therapies: pooled analysis of consecutive cohorts of the C-144-01 study. Journal for Immunotherapy of Cancer. 2022;10(12):12. DOI: https://dx.doi.org/10.1136/jitc-2022-005755.

[10] ESMO. ESMO score card lifileucel. [cited 15.05.2025]. Available from: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-for-solid-tumours/esmo-mcbs-scorecards?scorecard=430-1.

[11] ESMO. ESMO score card ipilimumab. Available from: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-for-solid-tumours/esmo-mcbs-scorecards?scorecard=90-1.

[12] ESMO. ESMO score card Nivolumab + ipilimumab. Available from: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-for-solid-tumours/esmo-mcbs-scorecards?scorecard=77-1.

[13] ESMO. ESMO score card Nivolumab + relatlimab. Available from: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-for-solid-tumours/esmo-mcbs-scorecards?scorecard=330-1.

[14] ESMO. ESMO score card Dabrafenib + trametinib. Available from: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-for-solid-tumours/esmo-mcbs-scorecards?scorecard=85-1.

[15] (IHE) I. o. H. E. Quality Appraisal of Case Series Studies Checklist. Edmonton (AB): Institute of Health Economics. 2014. Available from: https://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about.

[16] Guyatt G., Oxman A. D., Akl E. A., Kunz R., Vist G., Brozek J., et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-394. Epub 20101231. DOI: 10.1016/j.jclinepi.2010.04.026.

[17] Jansen J. P., Fleurence R., Devine B., Itzler R., Barrett A., Hawkins N., et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. Value Health. 2011;14(4):417-428. DOI: 10.1016/j.jval.2011.04.002.

[18] Hutton B., Salanti G., Caldwell D. M., Chaimani A., Schmid C. H., Cameron C., et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care

interventions: checklist and explanations. Ann Intern Med. 2015;162(11):777-784. DOI: 10.7326/M14-2385.

[19] Retel V. P., Steuten L. M. G., Geukes Foppen M. H., Mewes J. C., Lindenberg M. A., Haanen J., et al. Early cost-effectiveness of tumor infiltrating lymphocytes (TIL) for second line treatment in advanced melanoma: a model-based economic evaluation. BMC Cancer. 2018;18(1):895. Epub 20180915. DOI: 10.1186/s12885-018-4788-5.

[20] Ten Ham R. M. T., Rohaan M. W., Jedema I., Kessels R., Stegeman W., Scheepmaker W., et al. Cost-effectiveness of treating advanced melanoma with tumor-infiltrating lymphocytes based on an international randomized phase 3 clinical trial. Journal for Immunotherapy of Cancer. 2024;12(3). DOI: 10.1136/jitc-2023-008372.

[21] Rohaan M. W., Borch T. H., van den Berg J. H., Met O., Kessels R., Geukes Foppen M. H., et al. Tumor-Infiltrating Lymphocyte Therapy or Ipilimumab in Advanced Melanoma. New England Journal of Medicine. 2022;387(23):2113-2125. DOI: https://dx.doi.org/10.1056/NEJMoa2210233.

[22] STATISTIK AUSTRIA. Krebserkrankungen in Österreich 2024. 2024. Available from: https://www.statistik.at/fileadmin/publications/Krebs-2024_Webversion-barrierefrei_Rev1.pdf.

[23] European Federation of Pharmaceutical Industries and Associations. Immuno- & targeted therapy saving melanoma patient lives. 2025.

[24] Isaksson K., Katsarelias D., Mikiver R., Carneiro A., Ny L. and Olofsson Bagge R. A Population-Based Comparison of the AJCC 7th and AJCC 8th Editions for Patients Diagnosed with Stage III Cutaneous Malignant Melanoma in Sweden. Annals of Surgical Oncology. 2019;26(9):2839-2845. Epub 20190520. DOI: 10.1245/s10434-019-07448-y.

[25] Kralovicova K. K. D., Stanak M.,. Liečivo nivolumab (Opdivo) v monoterapii na liečbu pokročilého (neresektovateľnéhoalebo metastatického) melanómu. Hodnotenie pre Kategorizačnú komisiu číslo 12A. Bratislava: NIHO, 2023.

[26] Wolchok J. D., Chiarion-Sileni V., Gonzalez R., Grob J. J., Rutkowski P., Lao C. D., et al. Long-Term Outcomes With Nivolumab Plus Ipilimumab or Nivolumab Alone Versus Ipilimumab in Patients With Advanced Melanoma. Journal of Clinical Oncology. 2022;40(2):127-137. Epub 20211124. DOI: 10.1200/JCO.21.02229.

[27] Garbe C., Amaral T., Peris K., Hauschild A., Arenberger P., Basset-Seguin N., et al. European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment - Update 2024. European Journal of Cancer. 2025;215:115153. DOI: https://dx.doi.org/10.1016/j.ejca.2024.115153.

[28] Dummer R., Flaherty K. T., Robert C., Arance A., de Groot J. W. B., Garbe C., et al. COLUMBUS 5-Year Update: A Randomized, Open-Label, Phase III Trial of Encorafenib Plus Binimetinib Versus Vemurafenib or Encorafenib in Patients With BRAF V600-Mutant Melanoma. Journal of Clinical Oncology. 2022;40(36):4178-4188. Epub 20220721. DOI: 10.1200/JCO.21.02659.

[29] Betof Warner A., Hamid O., Komanduri K., Amaria R., Butler M. O., Haanen J., et al. Expert consensus guidelines on management and best practices for tumor-infiltrating lymphocyte cell therapy. Journal for Immunotherapy of Cancer. 2024;12(2):29. DOI: https://dx.doi.org/10.1136/jitc-2023-008735.

[30] U.S. National Library of Medicine and ClinicalTrials.gov. 2025 [cited 13.05.2025]. Available from: https://clinicaltrials.gov/.

[31] Forget M. A., Haymaker C., Hess K. R., Meng Y. J., Creasy C., Karpinets T., et al. Prospective Analysis of Adoptive TIL Therapy in Patients with Metastatic Melanoma: Response, Impact of Anti-CTLA4, and Biomarkers to Predict Clinical Outcome. Clinical Cancer Research. 2018;24(18):4416-4428. DOI: https://dx.doi.org/10.1158/1078-0432.CCR-17-3649.

[32] Khammari A., Nguyen J. M., Leccia M. T., Guillot B., Saiagh S., Pandolfino M. C., et al. Tumor infiltrating lymphocytes as adjuvant treatment in stage III melanoma patients with only one invaded lymph node after complete resection: results from a multicentre, randomized clinical phase III trial. Cancer Immunology, Immunotherapy. 2020;69(8):1663-1672. DOI: https://dx.doi.org/10.1007/s00262-020-02572-1.

[33] Fradley M. G., Damrongwatanasuk R., Chandrasekhar S., Alomar M., Kip K. E. and Sarnaik A. A. Cardiovascular Toxicity and Mortality Associated With Adoptive Cell Therapy and Tumor-infiltrating Lymphocytes for Advanced Stage Melanoma. Journal of Immunotherapy. 2021;44(2):86-89. DOI: https://dx.doi.org/10.1097/CJI.0000000000000341.

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH