Lifileucel for previously treated unresectable or metastatic melanoma

For Publication –information
REDACTED

Technology appraisal committee A [4 November 2025]

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Lifileucel for previously treated unresectable or metastatic melanoma

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling
- ❑ Other considerations
- ❑ Cost effectiveness results
- ❑ Summary

NICE National Institute for Health and Care Excellence

Background on unresectable or metastatic melanoma

Common cancer with historically low survival rates at advanced stages

Causes

- Modifiable: exposure to UV rays, sunburn
- Unmodifiable: various, including family history of melanoma, fair skin, blonde or red hair, chronic immunosuppression, multiple/atypical moles/birthmarks, age >65 years and male sex (with increasing age)

Epidemiology of melanoma

- Fifth most common cancer in the UK; 17,557 new cases per year on average[1]
- In UK, melanoma incidence rate has increased by 147% since early 1990s[1]

Diagnosis and classification: Stages 3 and 4 are the focus of this evaluation

- ~16% diagnosed at stage 3 and ~10% diagnosed at stage 4[2]

Symptoms and prognosis

- Early-stage melanoma largely asymptomatic; symptoms for metastatic disease depend on metastasis location
- Evidence suggests that long-term survival rates have improved since the introduction of immunotherapy[3]

Sources: (1) Cancer Research UK; (2) National Disease Registration Service; (3) Wolchock et al 2024

Abbreviations: UV, ultraviolet

Patient perspectives

Submission from Melanoma Focus and a patient expert

Living with melanoma

- Melanoma is an unpredictable cancer; people live from scan to scan with the fear of progression
- Symptoms can include weight loss, muscle pain, confusion, memory problems, mood or personality changes, feeling sick and extreme fatigue
- Currently available treatments can have long lasting side effects that have a severe impact on QoL and ability to perform everyday activities

Current care

- People with advanced treatment resistant melanoma have no other options available to them

Lifileucel

- Addresses an unmet need in a heavily pretreated population
- Is a one-time personalised treatment tailored to an individual's cancer that could have long term benefits and is potentially curative

"We need a treatment for advanced and for resistant melanoma. We need access to effective treatments… After TILs [e.g. lifileucel] there is less physical pain and panic about the future. Improved mood and less anxiety. "

"[Lifileucel] is brutal and uncomfortable for a short period but after, the freedom of not having to revolve around blood tests and infusions allows you a much better quality of life"

Abbreviations: QoL, Quality of life; TIL, Tumour infiltrating lymphocytes;

Clinical perspectives

Submissions from 2 clinical experts

Unmet need / current treatment options

- Current treatment options include enrolling in a clinical trial, chemotherapy or BSC, which consists of symptom management, palliative care, palliative radiotherapy, and emotional and practical support
- Current treatments are not effective in the refractory setting

Lifileucel

- Is the first approved cellular therapy for a solid tumour setting and has shown a durable benefit in about a third of refractory patients

Use in the NHS

- Delivering lifileucel is complex and intense and requires more resources than current standard of care
- Lifileucel should only be delivered in appropriately resourced centres → Centres may require support and mentoring from established centres and input with accreditation and licencing etc.

"[Lifileucel] will undoubtedly provide a tranche of patients with improvements over currently available care …. it would both increase length of life and quality for those who respond given the alternative would be ineffective chemotherapy or BSC for the majority."

"Acute toxicities are mainly from lymphodepleting chemotherapy and high-dose IL-2 … these are generally manageable with little significant long term toxicity seen."

Abbreviations: BSC, Best supportive care; IL-2, Interleukin-2;

Equality considerations

- Some people may not have easy access to treatment due to the geographic location of treatment centres
- Suitability of lifileucel for people with a learning or physical disabilities will need to be considered carefully to ensure it would be offered when appropriate
- Lifileucel is unsuitable for people who are pregnant
- Lifileucel is unsuitable for some older, frailer people (clinical expert noted this is true for many treatments)
- People under 18 were not included in the trial ([redacted])
    - ↳ A clinical expert considered that people under 18 would receive the same potential benefit as was observed in people over 18

Lifileucel (AMTAGVI, Iovance Biotherapeutics)

Lifileucel details

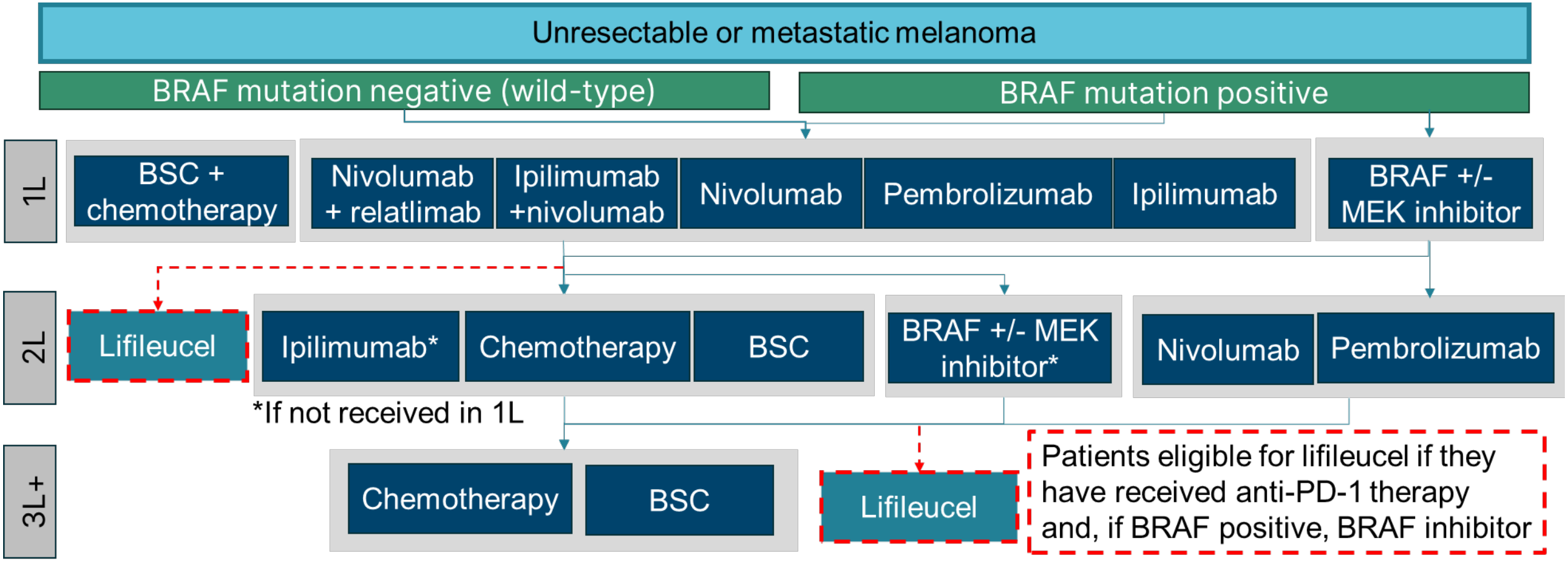
Marketing authorisation	• Anticipated marketing authorisation: [redacted] • Marketing authorisation not yet granted by MHRA; [redacted]
Mechanism of action	• Cell therapy: composed of CD4+ and CD8+ T-cells derived from patient's tumour tissue • Tumour-derived T-cells enter the tumour microenvironment and mediate tumour cell death through release of cytokines and cytolytic enzymes, promoting cell lysis
Administration*	• Melanoma lesion surgically resected; T-cell manufacturing and quality testing turnaround time ~33 days • Administered in 3-step procedure with an approximately 11-day duration: 1. Patient receives lymphodepletion chemotherapy regimen prior to receiving infusion 2. Lifileucel infused within 24-96 hours after last dose of chemotherapy 3. From 3-24 hours after lifileucel infusion, IL-2 infusion administered every 8-12 hours for up to 6 doses
Price	• List price per infusion and administration (one-time cost): [redacted] • A patient access scheme has been proposed

* See appendix – Steps and timelines for the administration of lifileucel

Abbreviations: BRAF, v-raf murine sarcoma viral oncogene homolog B1; IL-2, Interleukin-2; MEK, Mitogen-activated extracellular signal-regulated kinase; MHRA, Medicines and Healthcare products Regulatory Agency; PD-1, Programmed death 1;

Current UK treatment pathway and proposed positioning of lifileucel

Lifileucel proposed as 2L or 3L treatment, depending on BRAF status



Does this reflect the treatment pathway for unresectable or metastatic melanoma in the UK?
Is the proposed positioning for lifileucel appropriate?

Abbreviations: 1L, First line; 2L, Second line; 3L, Third line; BRAF, v-raf murine sarcoma viral oncogene homolog B1; BSC, Best supportive care; MEK, Mitogen-activated extracellular signal-regulated kinase; PD-1, Programmed death 1;

Key issues

Key issue if ipilimumab is a relevant comparator

Key issues for discussion	ICER impact
Comparators	High
Relative effectiveness of lifileucel vs comparators	
Lifileucel vs ipilimumab – uncertainty associated with STC	High
Lifileucel vs BSC – estimating efficacy of BSC by applying HR to chemotherapy model	Low
Extrapolation of effectiveness of lifileucel and comparators	
Appropriate mixture-cure model (MCM) parametric extrapolation for lifileucel	Low
Survival models for lifileucel (vs ipilimumab) – method of adjustment of MCM for lifileucel	High
Survival models for ipilimumab	High
Utility values	Low
Set-up, logistics, training and delivery costs for lifileucel	High
QALY weighting for severity	High

Other issues – not for discussion
Implementation of PSA
Outcomes for people in the lifileucel arm who do not receive lifileucel (see appendix)
Non-reference case discount rates (see appendix)

Abbreviations: BSC, Best supportive care; EAG, External Assessment Group; HR, Hazard ratio; ICER, Incremental cost-effectiveness ratio; MCM, Mixture-cure model; PSA, Probabilistic sensitivity analysis; QALY, Quality-adjusted life year; STC, Simulated treatment comparison;

Key issue: Comparators

See appendix – Company chemotherapy basket of regimens

Company: ipilimumab key comparator; EAG: BSC key comparator

Background

- Comparators in the NICE scope: ipilimumab monotherapy, chemotherapy (dacarbazine, temozolomide, paclitaxel, paclitaxel and carboplatin) and BSC

Company

- Ipilimumab is key comparator→ Clinical advice suggests not everyone receives nivolumab + ipilimumab at 1L, which leaves ipilimumab as an option at 2L (especially after 1L anti-PD1 monotherapies)
- Chemotherapy use is very low, clinical experts think its not very effective
  - ↳ Chemotherapy is modelled as a basket of regimens because individual data is not available → Clinical experts expect no difference in outcomes between individual chemotherapy regimens
- Clinical expert discussions: 50% receive ipilimumab 1L (+nivolumab), 50% will not receive ipilimumab 1L
  - ↳ TA950, clinical experts advised 20% of those who have pembrolizumab or nivolumab monotherapy 1L are expected to be prescribed ipilimumab monotherapy
- Modelled market share assumptions BSC: [redacted], Ipilimumab: [redacted], Chemotherapy: [redacted]

EAG comments

- BSC may be key comparator → Clinical advice suggests most receive BSC because those able to receive ipilimumab do so at 1L (with nivolumab) and chemotherapy rarely used due to limited effectiveness

What are the relevant comparators for lifileucel?

Abbreviations: 1L, First line; 2L, Second line; BSC, Best supportive care; EAG, External Assessment Group; PD-1, Programmed death 1;

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Key clinical trial: Study C-144-01

See appendix - Study design: C-144-01

Model uses pooled cohort 2 and 4 data from June 2023; final read out expected late 2025

	Study C-144-01 (NCT02360579)
Design	Phase II, open-label, multicohort, multicentre, single-arm study
Population	Adults with unresectable or metastatic melanoma who progressed following treatment on at least 1 systemic therapy, including a PD-1 blocking antibody, and if BRAF V600 mutation-positive, a BRAF inhibitor or BRAF inhibitor in combination with a MEK inhibitor
Cohort 1	Non-cryopreserved lifileucel (Not in clinical use)
Cohort 2 and 4	**Cryopreserved lifileucel***
Cohort 3	Retreatment of Cohort 1, 2 and 4 (Licence will not include retreatment)
Intervention	Lifileucel regimen
Comparator(s)	None (single-arm study)
Duration	4-year follow-up period (30th June 2023 DCO)
Primary outcome	ORR
Key secondary outcomes	PFS, OS, DOR, AEs, HRQoL
Locations	42 sites (Including 4 in the UK)
Used in model?	Yes, PDAwCS efficacy set (Cohorts 2 and 4 only)

*Cohorts 2 & 4 enrolled using the same eligibility criteria, during different timeframes but have different baseline characteristics

Abbreviations: AE, Adverse event; BRAF, v-raf murine sarcoma viral oncogene homolog B1; DCO, Data cut-off; DOR, Duration of response; HRQoL, Health-related quality of life; MEK, Mitogen-activated extracellular signal-regulated kinase; ORR, Objective response rate; OS, Overall survival; PD-1, Programmed death 1; PDAwCS, Pooled data aligned with commercial specifications; PFS, Progression-free survival;

Clinical trial results: Study C-144-01

- PDAwCS efficacy analysis set used in the model (Cohorts 2 and 4) → comprised only people that received lifileucel within proposed SmPC dosing range and produced at facilities approved for commercial manufacturing (median follow-up of [redacted])
- Compared with Cohort 2, Cohort 4 included a higher proportion of people with negative prognostic factors for survival: Stage 4 melanoma; >3 lesions, elevated LDH, and liver and/or brain metastasis
- Median OS was higher in Cohort 2 than Cohort 4

Key efficacy outcomes as assessed by IRC reported for PDAwCS efficacy set (DCO: June 2023)

	Cohort 4 (N=[redacted])	Cohort 2 (N=[redacted])	Pooled cohort 2 and 4 (N=[redacted])
Median OS, months (95% CI)	[redacted]	[redacted]	[redacted]
Median PFS, months (95% CI)	[redacted]	[redacted]	[redacted]

EAG

- Acknowledges differences between the 2 cohorts but considers that pooling the data is reasonable
- Single-arm trial design is a key methodological concern

- Is it reasonable to pool the data for Cohorts 2 and 4?
- Is the PDAwCS population generalisable to who is expected to receive lifileucel in clinical practice?

See appendix - Baseline characteristics C-144-01 Cohorts 2 and 4

See appendix - Key clinical trial results – C-144-01 OS and PFS KM plots

Abbreviations: CI, Confidence interval; DCO, Data cut-off; EAG, External Assessment Group; IRC, Independent Review Committee; LDH, lactate dehydrogenase; NR, Not reported; OS, Overall survival; PDAwCS, Pooled data aligned with commercial specifications; PFS, Progression-free survival; SmPC, Summary of Product Characteristics;

See appendix - ITC methodology

Key issue: Lifileucel vs ipilimumab - STC (1/2)

Simulated treatment comparison used to match populations in ITC

Background

- No direct evidence for lifileucel vs ipilimumab so company did an unanchored ITC → adjusted for population differences using simulated treatment comparison (STC) with da Silva 2021 informing outcomes for ipilimumab
- STC approach: statistical model fitted using IPD from Study C-144-01 with covariates*, the fitted model was then used to predict the outcomes for lifileucel that would have been observed if C-144-01 had the same baseline patient characteristics as the da Silva population

Overview of data source for each treatment

Treatment	Data source	N
Lifileucel	C-144-01 PDAwCS efficacy set	[redacted]
Ipilimumab	Da Silva et al 2021: • Real-world retrospective cohort study from 15 melanoma centres in Australia, Europe and US • Patients with metastatic melanoma (unresectable stage 3 and 4), resistant to anti-PD-L1	162

ITC results

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
OS	[redacted]	[redacted]
PFS	[redacted]	[redacted]

***Adjusts for:** age, sex, disease stage, ECOG PS and LDH levels

Abbreviations: CI, Confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, Hazard ratio; IPD, Individual patient data; ITC, Indirect treatment comparison; LDH, lactate dehydrogenase; OS, Overall survival; PD-1, Programmed death 1; PFS, Progression-free survival; STC, Simulated treatment comparison;

Key issue: Lifileucel vs ipilimumab - STC (2/2)

EAG: STC results should be interpreted with caution

EAG comments

- Concerned about robustness of STC results → results are highly dependent on whether LDH included as a covariate
- Possible that all effect modifiers and prognostic factors are not accounted for which potentially introduces bias
- Relative treatment effects estimated in the da Silva (older but more fit) population, which differs from Study C-144-01 population (that is assumed to reflect the population that would receive lifileucel in the NHS) so unclear if effects are applicable to target population for this appraisal
- Company used data manipulation techniques to address discrepancies in baseline characteristics, which may have made the simulated population slightly healthier than even the da Silva population
- A MAIC analysis would provide further justification for the STC results and may reduce uncertainty
  - ↳ Acknowledged MAICs suffer from a large reduction in sample size when the degree of overlap is poor

- Does the da Silva population reflect the relevant population?
- Were all relevant prognostic factors & treatment effect modifiers captured?
- Are the outputs from the company's STC clinically plausible?

See appendix – Baseline characteristics of studies used in the STC (1/3)

Abbreviations: BRAF, v-raf murine sarcoma viral oncogene homolog B1; EAG, External Assessment Group; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LDH, Lactate dehydrogenase; MAIC, Matching-adjusted indirect comparison; STC, Simulated treatment comparison;

Lifileucel vs chemotherapy – Naïve comparison (1/2)

Relative effect for lifileucel vs chemotherapy based on a naïve unadjusted ITC

Company

- Mangin et al 2021 was only study identified to inform the chemotherapy population
- Population adjusted ITC analyses ruled out due to small sample size
- Naïve unadjusted ITC was performed → acknowledged limitations of unadjusted comparisons
- Lifileucel population (C-144-01) appear fitter than the chemotherapy population (Mangin et al.)

Overview of data source for each treatment

Treatment	Data source	N
Lifileucel	C-144-01 PDAwCS efficacy set	[redacted]
Chemotherapy	Mangin et al 2021: • Real-world retrospective cohort study from single centre in France • Patients with unresectable stage 3/4 metastatic melanoma who received 1L treatment with PD-L1 inhibitor or BRAF/MEK inhibitor	50

Naïve ITC results

	OS	PFS
Unadjusted HR (95% CI)	[redacted]	[redacted]

See appendix – Unadjusted KM curves lifileucel v chemotherapy for PFS and OS

See appendix – Baseline characteristics of studies in naïve comparison

Abbreviations: 1L, First line; BRAF, v-raf murine sarcoma viral oncogene homolog B1; CI, Confidence interval; HR, Hazard ratio; ITC, Indirect treatment comparison; KM, Kaplan-Meier; MEK, Mitogen-activated extracellular signal-regulated kinase; OS, Overall survival; PD-1, Programmed death 1; PDAwCS, Pooled data aligned with commercial specifications; PFS, Progression-free survival;

Lifileucel vs chemotherapy – Naïve comparison (2/2)

EAG comments:

- Naïve comparison fails to account for chemotherapy population being less fit than the lifileucel population
- Expects that had the company adjusted for differences between populations, the relative treatment effect would be smaller than in the unadjusted analysis
  - ↳ On average, Study C-144-01 participants were younger and less frail based on median age and the proportion of patients with an ECOG score of 0 or 1
  - ↳ Study C-144-01 has a higher proportion of people with normal LDH levels and a lower proportion of people with brain metastases
- Limited overlap in several covariates between Study C-144-01 and Mangin et al (in particular ECOG)
  - ↳ Population adjustment using an STC would not fully address this overlap issue

NICE Technical team comments:

NICE methods manual (section 3.4.20): *"It is not acceptable to compare results from single treatment arms from different randomised trials. If this type of comparison is presented, the data will be treated as observational in nature and associated with increased uncertainty."*

Is the unadjusted ITC for lifileucel vs chemotherapy suitable for decision making?

Abbreviations: BSC, Best supportive care; EAG, External Assessment Group; HR, Hazard ratio; N/A, Not applicable; OS, Overall survival; PDAwCS, Pooled data aligned with commercial specifications; PFS, Progression-free survival;

Key issue: Lifileucel vs BSC – applying HR to chemo model

Relative treatment effect for lifileucel vs BSC based on adjusting chemotherapy models

Company

- No studies identified reporting PFS or OS for people receiving BSC
- HR for BSC of 2.0 vs chemotherapy based on structured elicitation exercise with clinical experts

Overview of data source for each treatment

Treatment	Data source	N
Lifileucel	C-144-01 PDAwCS efficacy set	[redacted]
BSC	Structured elicitation exercise with clinical experts	N/A

Preferred HR for BSC vs chemotherapy

	Company	EAG
OS & PFS	2.0	1.0

EAG comments

- Unspecified number of company clinical experts considered "*chemotherapy was about the same as giving no treatment*" → EAG clinical experts agreed outcomes for BSC expected to be similar to chemotherapy
- Unclear what questions were asked during structured elicitation exercise and how potential conflicting views were accounted for
- Outcomes for BSC highly uncertain but further clinical opinion may help estimate the most plausible outcomes

- Is it appropriate to assume same OS and PFS for BSC and chemotherapy?
- What is committee's preferred approach to modelling relative treatment effects for lifileucel vs BSC?

Abbreviations: BSC, best supportive care; EAG, external assessment group; HR, hazard ratio; PFS, progression-free survival; OS, overall survival; SLR, systematic literature review

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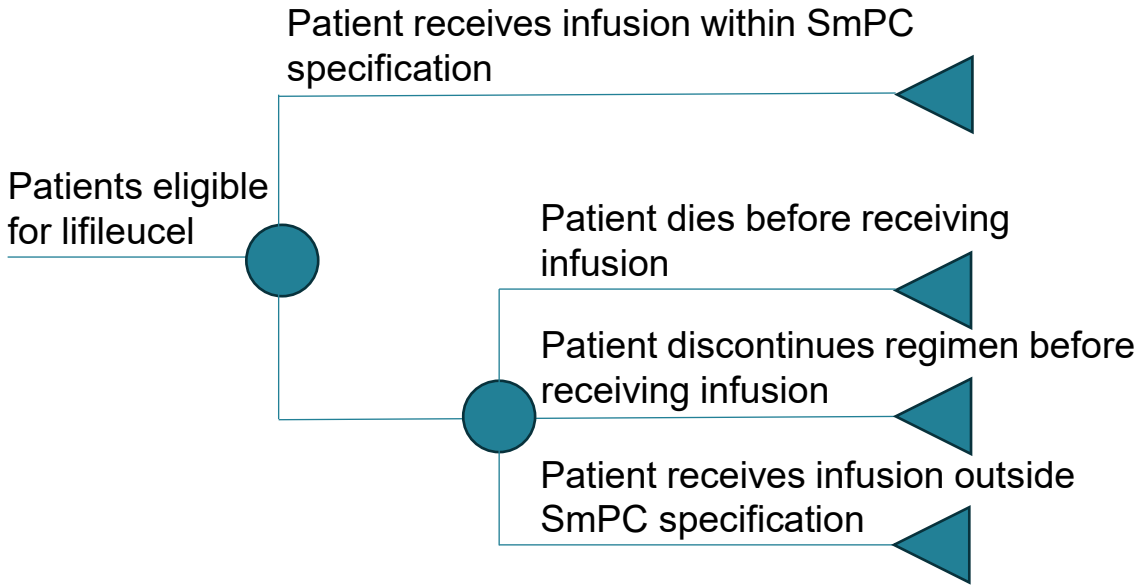
Overview of company's model

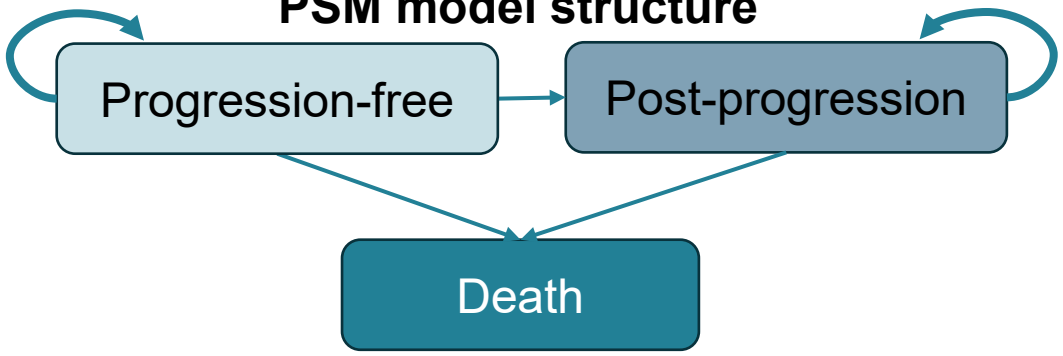
Partitioned survival model with initial decision tree component for lifileucel

Decision tree for people eligible for lifileucel



* See appendix – Lifileucel treatment proportion receiving regimen

PSM model structure



Lifileucel affects **QALYs** by:

- Extending OS & PFS, including the potential for cure in a proportion of patients
- Slightly increasing QALY losses associated with AEs

Lifileucel affects **costs** by:

- Increasing drug acquisition and administration costs associated with the lifileucel regimen
- Increasing health state costs due to extended OS
- Slightly increasing expected costs of managing AEs

Assumptions with an impact on ICER:

- Approach used to model relative & absolute effects of lifileucel vs ipilimumab
- MCMs for lifileucel PFS and OS
- Inclusion of the NHS England CAR-T tariff
- Severity modifier for ipilimumab comparison
- Choice of discount rate

Abbreviations: AE, Adverse event; CAR-T, Chimeric antigen receptor T-cell; ICER, Incremental cost-effectiveness ratio; MCM, Mixture-cure model; OS, Overall survival; PFS, Progression-free survival; QALY, Quality-adjusted life year; SmPC, Summary of Product Characteristics;

Lifileucel and ipilimumab survival models

Company uses MCM only for lifileucel; comparators use standard parametric models

Mixture cure model (MCM):

Population comprised of 2 discrete groups:

1) People who are cured and will not progress or die from disease → long-term survival similar to general population
   - ↳ General population mortality adjusted by a standardised mortality ratio [SMR] from receiving a treatment throughout the lifetime horizon (SMR=1.0 in Company and EAG base case; scenario SMR=1.57)
   - ↳ The proportion cured is determined by a cure fraction, estimated through the model-fitting procedure
2) People who are not cured and who have a continued risk of progression and or death due to their disease

Overview of data sources, and modelling approaches used for each treatment

Treatment	Company	EAG
Lifileucel vs Ipilimumab*	MCMs fitted to C-144-01 data and uplifted using ratio of STC-adjusted & unadjusted HRs ("Adjusted" MCMs)	MCMs fitted to C-144-01 data ("Unadjusted" MCM)
Ipilimumab	Standard parametric models fitted to da Silva et al. data	Inverse STC-adjusted HR applied to the lifileucel MCMs

* For lifileucel vs chemotherapy or BSC both the company and EAG use MCMs fitted to C-144-01 data ("Unadjusted" MCM) to model lifileucel survival

NICE Abbreviations: BSC, Best supportive care; EAG, External Assessment Group; HR, Hazard ratio; MCM, Mixture-cure model; SMR, Standardised mortality ratio; STC, Simulated treatment comparison;

Key issue: Lifileucel MCM selection

Company: exponential for OS & log-normal for PFS; EAG: log-logistic for OS & PFS

Company

- After lifileucel, some are cured of disease (shown by plateau in PFS & OS KM curves), so MCMs appropriate
- **OS base case: exponential MCM (scenario log-logistic MCM)** → Supported by clinicians, best statistical fit and clinically intuitive (assumes uncured population die at a constant rate)
- **PFS base case: log-normal MCM (scenarios log-logistic & exponential MCMs)** → Supported by clinicians, observed and predicted hazards aligned with and reached general population OS hazards

EAG comments

- **OS preferred analysis: log-logistic MCM** → comparable fit to exponential MCM, cure fraction closely aligns with expected cure fraction suggested by clinicians at the company's advisory board meeting ([redacted]) and produces a more clinically plausible difference between the PFS & OS cure fraction estimates ([redacted])
  - ↳ OS exponential MCM suggests cure fraction considered by 1 of company's clinical experts to be "too high" and leads to [redacted] PFS & OS cure fractions difference despite no effective therapies post progression
- **PFS preferred analysis: log-logistic MCM (scenario log-normal MCM)** → Best-fitting distribution; aligns with preferences of clinical experts in the 1 to 1 meetings held by the company

Estimated lifileucel OS cure fractions

MCM	Estimated cure fraction
Exponential	[redacted]
Log-logistic	[redacted]

Estimated lifileucel PFS cure fractions

MCM	Estimated cure fraction
Log-normal	[redacted]
Log-logistic	[redacted]

What is committee's preferred MCM for lifileucel OS & PFS?

Abbreviations: EAG, External Assessment Group; KM, Kaplan-Meier; MCM, Mixture-cure model; OS, Overall survival; PFS, Progression-free survival;

Key issue: Survival models for lifileucel (vs ipilimumab)

- Company: uplifts lifileucel MCM to estimate effect if lifileucel used in da Silva population & uses standard parametric models for ipilimumab
- EAG: prefers unadjusted MCM for lifileucel & STC-adjusted lifileucel MCM for ipilimumab

Company Base case (lifileucel vs ipilimumab): Lifileucel PFS & OS MCMs uplifted to the power of the ratio of STC adjusted & unadjusted HRs to estimate outcomes in the da Silva population for lifileucel

- Unadjusted lifileucel curve used as the base for adjustments as it has the longest follow up
  ↳ STC adjusted curve has shorter follow-up and is influenced by the ipilimumab curve shape (no plateau)

EAG comments Preferred analysis (all comparisons): Lifileucel PFS & OS unadjusted MCMs

- Reflects outcomes for lifileucel in C-144-01 (the target population) and associated implied cure fractions (PFS: [redacted] OS: [redacted]) more closely aligned with company clinical expert expectations ([redacted])
- Company approach estimates treatment effects in the wrong (da Silva) population and generates implausible implied cure fractions (PFS: [redacted] OS: [redacted]) substantially higher than estimated using study data

Lifileucel OS cure fractions (Company base case)

MCM	Cure fraction from MCM	Cure fraction after STC adjustment
Exponential	[redacted]	[redacted]

Lifileucel PFS cure fractions (Company base case)

MCM	Cure fraction from MCM	Cure fraction after STC adjustment
Log-normal	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; HR, Hazard ratio; MCM, Mixture-cure model; OS, Overall survival; PFS, Progression-free survival; STC, Simulated treatment comparison;

Key issue: Survival models for ipilimumab (1/4)

Company uses standard parametric model fitted to da Silva data, plus cure after 3 years treatment for ipilimumab

Company

Ipilimumab PFS & OS standard parametric models fitted directly to data from da Silva et al

- Model assumes people who are progression free at 3-years are cured ([redacted] of people who receive ipilimumab are subject to general population mortality risk after 3-years)
- Standard parametric model modelling was most appropriate approach given the short follow up time (22.1 months) and was validated by clinical experts
- MCM approach not appropriate due to short follow-up → ipilimumab OS KM showed no flattening and the PFS KM curve showed a small plateau at approximately 15 to 19 months
- Spline based modelling could not be conducted in the time provided to respond to clarification questions
- Studies suggest that proportion of people that receive ipilimumab and experience long-term survival is close to 0% (see appendix – Studies identified by the company (1/2))
- Clinical experts optimistically estimated that 1-5% of people that receive ipilimumab would experience long-term survival (dependent on distribution of prior lines of treatment)

Abbreviations: KM, Kaplan-Meier; MCM, Mixture-cure model; OS, Overall survival; PFS, Progression-free survival;

Key issue if ipilimumab is a relevant comparator

See appendix - Ipilimumab survival extrapolations

Key issue: Survival models ipilimumab (2/4)

EAG prefers STC-adjusted lifileucel MCM for ipilimumab

EAG comments

Ipilimumab PFS & OS estimated by applying inverse STC-adjusted HR to the lifileucel MCMs

- EAG clinical experts expect that some people will achieve long-term survival after ipilimumab
- Preferred approach results in a plateau in model-predicted ipilimumab OS & PFS indicating outcomes similar to cure for a small proportion of people that receive ipilimumab, consistent with clinical opinion
- Long-term OS estimated using standard parametric models likely to have been underestimated, none of the models aligned with clinical expectations of cure for some people
- Despite the 3-year OS cure assumption, the company model predicts most people have progressed by this point and risk of progression is assumed to continue despite cure being assumed for OS
- Flexible models (e.g. spline models or MCMs) may have been better able to reflect the shape of the underlying hazards in the observed data

Abbreviations: EAG, External Assessment Group; HR, Hazard ratio; MCM, Mixture-cure model; OS, Overall survival; PFS, Progression-free survival; STC, Simulated treatment comparison;

Key issue: Survival models ipilimumab (3/4)

Alternative ipilimumab PFS and OS estimates based on company base case and EAG preferred analysis

[redacted]

Abbreviations: EAG, External Assessment Group; HR, Hazard ratio; MCM, Mixture-cure model; OS, Overall survival; PFS, Progression-free survival; STC, Simulated treatment comparison;

Key issue: Survival models ipilimumab (4/4)

Suggested approaches for modelling the relative treatment effect of lifileucel vs ipilimumab

Company	EAG
Lifileucel: PFS & OS MCMs uplifted to the power of the ratio of STC adjusted & unadjusted HRs to estimate outcomes in the da Silva population for lifileucel **Ipilimumab:** PFS & OS standard parametric models	**Lifileucel:** PFS & OS unadjusted MCMs **Ipilimumab:** PFS & OS estimated by applying the inverse STC-adjusted HR to the lifileucel MCMs

What is committee's preferred approach to modelling relative treatment effects of lifileucel vs ipilimumab?

Abbreviations: EAG, External Assessment Group; HR, Hazard ratio; MCM, Mixture-cure model; OS, Overall survival; PFS, Progression-free survival; STC, Simulated treatment comparison;

Key issue: Utility values

See appendix - Utility values

- Company: uses unweighted mean of 12 sources to estimate PF and PD utilities
- EAG: uses company approach, but notes should be interpreted with caution

Background

- Values in model based on unweighted mean values from 2 studies and 10 TAs in advanced melanoma
  - ↳ Progression free (PF): 0.77; Progressed disease (PD): 0.67
- Disutility due to lifileucel administration (applied in the first model cycle duration of 1 week): -0.09

Company

- QoL data collection in C-144-01 was not systematic and data was not robust
- Non-EQ-5D values included in unweighted mean to ensure all relevant and available data was considered; unweighted approach avoids privileging one study over another
- Scenario analysis conducted:
  1. Using the sources with the highest and lowest PF utility values
  2. Excluding non-EQ-5D utility values

EAG comments

- Company's approach unconventional and uses PD values from 1L, not necessarily applicable for PF at 2L
- But, no source provides utilities that are both clinically plausible and fully adhere to NICE reference case
- Scenarios conducted show minimal impact on ICER

Is the company's approach to estimating utility values acceptable for decision making?

Abbreviations: 1L, First line; 2L, Second line; EQ-5D, Euroqol 5-Dimensions; PD, Progressed disease; PF, Progression free; QoL, Quality of life; TA, Technology appraisal

Key issue: Set-up, logistics, training and delivery costs (1/2)

- Company: resource associated with lifileucel appropriately incorporated into model
- EAG: CAR-T tariff applied; replaces some resources already included

Company

- Modelled lifileucel administration costs included tumour tissue procurement, lymphodepletion infusion, lifileucel treatment and inpatient / ICU costs post-administration
- Inpatient / ICU costs post-administration were conservative (8 days on a general ward and 2 ICU days)
- Inclusion of logistics support, training and operational support costs not necessary
  - ↳ Hospitals that provide lifileucel will have existing cell therapy capabilities so should not require additional staffing support and training is also provided by the company for no charge

EAG comments

- Model may not fully reflect set-up, logistics, training and delivery costs
- **Base case: Included NHSE 2025/26 CAR-T tariff cost (£60,462) for all people that received lifileucel (both in line with the SmPC specification and out-of-specification)**
  - ↳ Assumed to cover cost of tumour tissue procurement, LD chemo admin, IL-2 admin and monitoring, AEs, 100 days of disease management and other NHS costs relating to set-up and delivery
- NHSE requests that the 2025/26 CAR-T tariff be included in the model

Abbreviations: AE, Adverse event; CAR-T, Chimeric antigen receptor T-cell; EAG, External Assessment Group; ICU, Intensive care unit; IL-2, Interleukin-2; LD, Lymphodepletion; NHSE, NHS England; SmPC, Summary of Product Characteristics;

Key issue: Set-up, logistics, training and delivery costs (2/2)

NHSE: committed to commissioning lifileucel activity at cost of CAR-T tariff (£60,863), if recommended

NHSE comments

- *"[NHSE] considers that the resource requirements to safely administer CAR-Ts and lifileucel are broadly comparable. What might not apply for lifileucel to the CAR-T tariff (some of the later immune complications) is at least offset by the need to invest in staff costs in the melanoma teams. Although there will be some sharing of inpatient lifileucel care with the current CAR-T teams, the use of the CAR-T tariff will be partly used to provide the melanoma personnel in order for true joint care to function and keep the patient safe."*
- CAR-T tariff proposed as a proxy for administration costs because there is limited evidence of what the costs in clinical practice are likely to be, and CAR-T is the most similar therapy to lifileucel actively commissioned in the NHS
- To give providers some certainty around income for the implementation phase, NHSE is committed to commissioning lifileucel at the level equivalent to CAR-T tariff if recommended (with subsequent cost data collection and review)
- CAR-T tariff has increased slightly (£60,863) to reflect the outcome of the 2025/26 pay awards

How should set-up, logistics, training and delivery costs be included in the model?

See appendix - Components of CAR-T tariff

Abbreviations: CAR-T, Chimeric antigen receptor T-cell; NHSE, NHS England;

Lifileucel for previously treated unresectable or metastatic melanoma

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling
- ✓ **Other considerations**
- ❑ Cost effectiveness results
- ❑ Summary

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Key issue: QALY weighting for severity (1/2)

Company and EAG disagree on severity modifier for comparison with ipilimumab

Company

Base case: modifier of 1.7 for all comparators

- Age ([redacted] years) and sex distribution ([redacted] female), aligned with the base case, taken from C-144-01
- Ipilimumab treated QALYs are optimistic
- Ipilimumab proportional QALY shortfall ([redacted]) close to the ≥95% threshold (for 1.7 modifier)
- Accounting for estimated usage of comparators lifileucel would qualify for an overall modifier of 1.7

EAG comments

Base case: modifier of 1.7 for BSC / chemotherapy and 1.2 for ipilimumab

- Company underestimates ipilimumab survival as they do not fully reflect expectations of cure for some
  - ↳ EAG preferred analyses including more optimistic ipilimumab survival estimate are also associated with a decision modifier of 1.2
- The company's model estimates pairwise ICERs against individual comparator, using a blended comparator for the modifier would introduce inconsistency between the approaches
- QALY weighting calculations and modelled ICERs are sensitive to the age and sex distribution used
  - ↳ Clinical advisors commented that people in Study C-144-01 were broadly representative of those who would be considered eligible to receive this treatment in NHS practice

Abbreviations: AS, Absolute shortfall; BSC, Best supportive care; DSU, Decision Support Unit; EAG, External Assessment Group; ICER, Incremental cost-effectiveness

Key issue: QALY weighting for severity (2/2)

Table: Absolute and proportional shortfall estimates for all comparators based on York Shortfall Calculator **(Based on company base case assumptions)**

Comparator	Mean QALYs for comparator	Absolute shortfall	Proportional shortfall	Severity modifier
Ipilimumab	0.88	13.47	93.87%	1.2
Chemotherapy	0.56	13.79	96.10%	1.7
BSC	0.29	14.06	97.98%	1.7

- Does the age and sex distribution from Study C-144-01 reflect the population that would receive lifileucel in the NHS?
- Should a x1.2 or a x1.7 QALY weighting for severity be applied for the comparison with ipilimumab?

Abbreviations: BSC, Best supportive care; QALY, Quality-adjusted life year;

Lifileucel for previously treated unresectable or metastatic melanoma

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling
- ❑ Other considerations
- ✓ **Cost effectiveness results**
- ❑ Summary

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Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential

comparator prices

- Cost effectiveness results include the correction of model errors identified by the EAG
- Only deterministic cost effectiveness results are presented because the EAG considers the results of the deterministic model to be more reliable due to problems in the company's probabilistic model
- Only pairwise comparisons are presented because the model includes adjustments in the comparison of lifileucel vs ipilimumab, but no adjustment for the comparisons against chemotherapy and BSC

Abbreviations: EAG, External Assessment Group; ICER, Incremental cost-effectiveness ratio;

Lifileucel for previously treated unresectable or metastatic melanoma

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling
- ❑ Other considerations
- ❑ Cost effectiveness results
- ✓ **Summary**

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Summary of company and EAG base case assumptions

Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Preferred HR for BSC vs chemotherapy	2.0	1.0
Lifileucel MCM	OS: Exponential, PFS: Log-normal	OS: Log-logistic, PFS: Log-logistic
Survival models lifileucel	PFS & OS MCMs uplifted to the power of the ratio of STC adjusted & unadjusted HRs	PFS & OS unadjusted MCMs
Survival models ipilimumab	PFS & OS standard parametric models	PFS & OS estimated by applying the inverse STC-adjusted HR to the lifileucel MCMs
Utility values	Unweighted mean values from 2 published studies and 10 TAs	
CAR-T tariff	Not included	Included
Cure time	3 years progression-free	5 years progression-free
Tumour procurement costs	Weighted based on number of finished consultant episodes from NHS national cost collection data	Weighted based on proportion of patients having the tumour resection at each site from Study C-144-01
QALY weighting	1.7 all comparisons	1.7 BSC & chemotherapy, 1.2 ipilimumab

Abbreviations: BSC, Best supportive care; CAR-T, Chimeric antigen receptor T-cell; EAG, External Assessment Group; HR, Hazard ratio; MCM, Mixture-cure model; OS, Overall survival; PFS, Progression-free survival; QALY, Quality-adjusted life year; STC, Simulated treatment comparison; TA, Technology appraisal;

Lifileucel for previously treated unresectable or metastatic melanoma

Supplementary appendix

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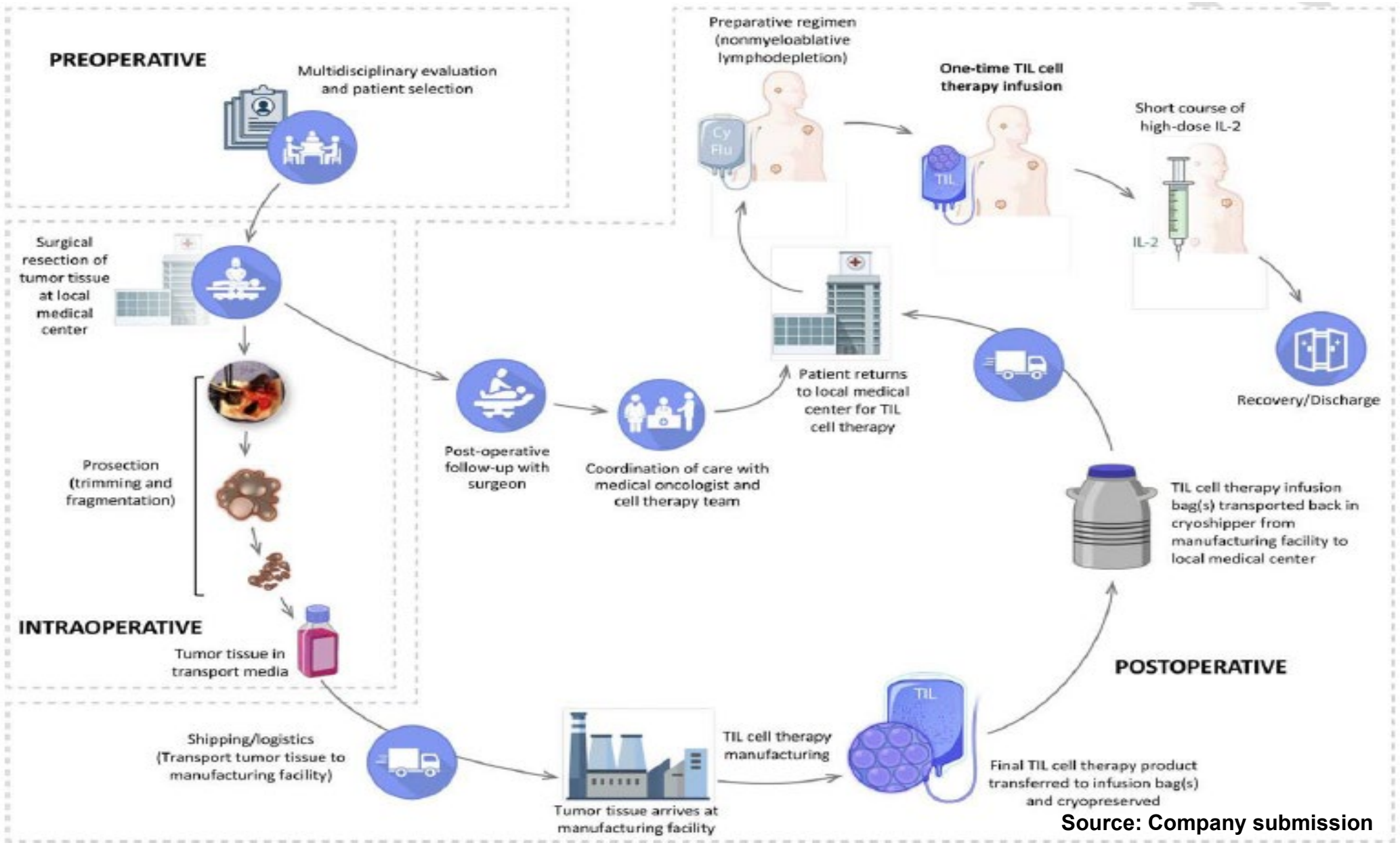
Link to- Lifileucel (AMTAGVI, Iovance Biotherapeutics)

Steps and timelines for the administration of lifileucel



Source: Company submission

Link to- Comparators

Company chemotherapy basket of regimens

Summary of chemotherapy regimens and weightings in company basket

Treatment	Dosage regimen*	Weighting**
Dacarbazine only	850mg/m^2 on day 1 and then once every 3 weeks	65%
Temozolomide only	200 mg/m^2 orally for 5 days every 4 weeks	10%
Carboplatin only	AUC 5 every 3 weeks	5%
Carboplatin + Paclitaxel	**Carboplatin:** -Cycle 1-4: AUC 5 on day 1 of each 21-day cycle -Cycle 5-10: AUC 5 on day 1 of each 21-day cycle **Paclitaxel:** -All cycles: 125mg/m^2 on day 1 of each 21-day cycle	10%
Dacarbazine + Cisplatin	**Dacarbazine:** -350 mg/m^2/day on day 1 every 21-day cycle for 4 cycles **Cisplatin:** -50 mg/m^2/day on days 1 every 21-day cycle for 4 cycles	10%

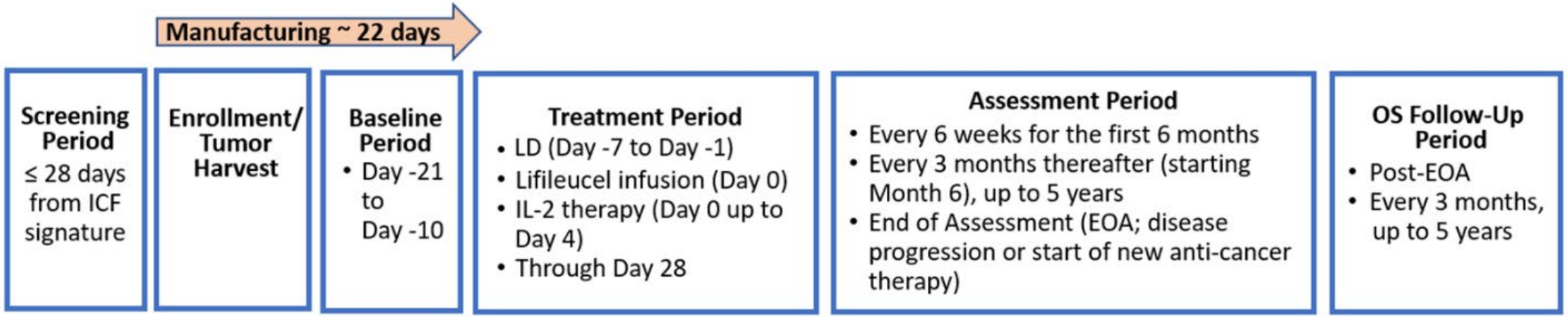
*Median time duration of 1.49 months from Mangin *et al.* (2021) was assumed for all chemotherapy regimen, **Lifileucel Advisory Board Report 2024 and 2025

EAG comments

- Minutes of the company's clinical advisory board meeting do not specifically record the view that individual chemotherapy regimens have equivalent efficacy
- Clinical advisors commented that all regimens have limited effectiveness and that they would expect that most patients (around 80-90%) would receive dacarbazine over other chemotherapy regimens
- There are differences between the regimens in the scope and those included in the company's basket
  - Paclitaxel monotherapy excluded but carboplatin monotherapy and dacarbazine + cisplatin included
  - Considered a minor discrepancy likely to have only a limited impact on the model results

Study design: C-144-01

Link to - Key clinical trial: Study C-144-01



Note: Cohort 3 patients (i.e., patients who were previously treated in Cohort 1,2, or 4 had progressed, and opted to be retreated with the lifileucel regimen) may have had a second tumour resection, if needed, especially when new lesions were available and feasible for resection.

Link to - Clinical trial results: Study C-144-01

Key clinical trial results – C-144-01 OS and PFS KM plots

Figure: KM curve PFS, assessed by the IRC for the PDAwCS efficacy set

Figure: KM curve OS, assessed by investigator for the PDAwCS efficacy set

Link to - Clinical trial results: Study C-144-01

Baseline characteristics C-144-01 Cohorts 4 and 2 (1/2)

Baseline disease characteristics for the PDAwCS efficacy set

Characteristics	Cohort 4 [redacted]	Cohort 2 [redacted]	Pooled Cohorts 2 and 4 [redacted]
Male, n (%)	[redacted]	[redacted]	[redacted]
Mean age (SD)	[redacted]	[redacted]	[redacted]
Baseline ECOG Score n (%)			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
≥2	[redacted]	[redacted]	[redacted]
BRAF status, n (%)			
Positive	[redacted]	[redacted]	[redacted]
Negative	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Mean number of prior therapies (SD)	[redacted]	[redacted]	[redacted]

Link to - Clinical trial results: Study C-144-01

Baseline characteristics C-144-01 Cohorts 4 and 2 (2/2)

Baseline disease characteristics for the PDAwCS efficacy set

Characteristics	Cohort 4 [redacted]	Cohort 2 [redacted]	Pooled Cohorts 2 and 4 [redacted]
Patients with baseline Liver and/or Brain Lesions by IRC, n (%)	[redacted]	[redacted]	[redacted]
Stage at study entry, n (%)			
IIIC	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]
Baseline LDH (U/L), n (%)			
<ULN	[redacted]	[redacted]	[redacted]
>1 - ≤ 2 x ULN	[redacted]	[redacted]	[redacted]
> 2 x ULN	[redacted]	[redacted]	[redacted]
Number of Baseline Target and Non-target Lesions Assessed by IRC, n (%)			
≤3	[redacted]	[redacted]	[redacted]
>3	[redacted]	[redacted]	[redacted]

Link to - Lifileucel vs ipilimumab - STC (1/2)

Company lifileucel vs ipilimumab ITC methodology

Background

- Company: STC may provide more accurate estimates than a MAIC where there is poor overlap in baseline characteristics across datasets

The STC analysis included three key steps:

1. A Cox regression model was fitted to the IPD in Study C-144-0128 with selected effect modifiers and prognostic variables (age, sex, disease stage, ECOG PS and LDH levels)
2. The survival probabilities after simulating patient-level covariates were predicted based on the reported patient characteristics in the da Silva 2021 study
    i. Adjusted Kaplan-Meier curves and pseudo-IPD for the comparator da Silva population receiving lifileucel were then obtained from the predicted survival probabilities
3. The hazard ratios were calculated for the comparator da Silva population based on the reconstructed pseudo-IPD from the predicted survival probabilities in the second step and the reconstructed pseudo-IPD from the published da Silva study

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; IPD, individual patient-level data; ITC, indirect treatment comparison; LDH, lactate dehydrogenase; MAIC, matching-adjusted indirect comparison; OS, overall survival;; PFS, progression-free survival; STC, simulated treatment comparison

Link to - Lifileucel vs ipilimumab - STC (2/2)

Baseline characteristics of studies used in the STC (1/3)

Baseline characteristics (Lifileucel: C-144-01, Ipilimumab: da Silva et al)

Characteristic	C-144-01 Pooled Cohorts 2 and 4 [redacted]	da Silva *et al.* (2021) ipilimumab group (N=162)	Is a greater treatment effect expected after adjusting?	Adjusted for?
Age, median (range)	[redacted]	67.0 (58-74)	**No** (the da Silva population appeared to be older)	**Yes** (based on company's assumption of 70 patients at age of 58, 70 patients at age of 74 and 22 patients at age of 67 years)
Sex, n (%):			**Unknown** (likely small or no impact)	**Yes** (assuming that 64% of male and 36% of female)
Male	[redacted]	103 (64)		
Female	[redacted]	59 (36)		
Disease stage, n (%):			**Unknown** (**No.** If at least one of the [redacted] Stage IV patients are at Stage IV M1a/M1b, this would mean that the da Silva population has a higher proportion of patients at late stage)	**Yes** (assuming that 27% of patients are at disease stage IIIC and 73% of patients are at disease stage IV)
IIIC	[redacted]	-		
IV	[redacted]	-		
III/M1a/M1b (if further specified)	[redacted]	44 (27)		
M1c/M1d (if further specified)	[redacted]	118 (73)		
IV (not further specified)	[redacted]	-		

Link to - Lifileucel vs ipilimumab - STC (2/2)

Baseline characteristics of studies used in the STC (2/3)

Baseline characteristics (Lifileucel: C-144-01, Ipilimumab: da Silva et al)

Characteristic	C-144-01 Pooled Cohorts 2 and 4 [redacted]	da Silva *et al.* (2021) ipilimumab group (N=162)	Is a greater treatment effect expected after adjusting?	Adjusted for?
ECOG score, n (%):			**No** (the da Silva population has a higher proportion of patients with ECOG score 1 or above)	**Yes** (based on company's assumption that 41% of patients have ECOG score of 0 and 59% of patients have ECOG score of 1)
0	[redacted]	64 (39.5)		
1	[redacted]	88 (54.3)		
≥2	[redacted]	7 (4.3)		
LDH level (U/L), n (%):			**Yes** (the da Silva population has a lower proportion of patients with high LDH)	**Yes** (assuming that 63% of patients have normal LDH level and 37% of patients have high LDH level)
≤ULN/Normal	[redacted]	95 (62.5)		
>ULN	[redacted]	57 (37.5)		
BRAF status, n (%):			**Yes** (the additional scenario analysis suggests that adjusting for BRAF status gives a slightly larger treatment effect for both PFS and OS)	**No** (only included in the additional analysis requested by EAG)
Mutated	[redacted]	34 (21)		
Wild type	[redacted]	102 (63)		
Other	[redacted]	26 (16)		
Unknown	[redacted]	0		

Link to - Lifileucel vs ipilimumab - STC (2/2)

Baseline characteristics of studies used in the STC (3/3)

Baseline characteristics (Lifileucel: C-144-01, Ipilimumab: da Silva et al)

Characteristic	C-144-01 Pooled Cohorts 2 and 4 [redacted]	da Silva *et al.* (2021) ipilimumab group (N=162)	Is a greater treatment effect expected after adjusting?	Adjusted for?
Melanoma subtype, n (%)			**Unknown**	**No**
Cutaneous	[redacted]	NR		
Mucosal	[redacted]	13 (8.0)		
Acral	[redacted]	20 (12.3)		
SSM	[redacted]	49 (30.3)		
Nodular	[redacted]	27 (16.7)		
Metastases, n (%)			**Unknown**	**No**
Liver	[redacted]	55 (34.0)		
Brain	[redacted]	43 (26.5)		
Time from last prior anti-PD-(L)1, median (range)	[redacted]	3.0 months (1.0-24.4)		

Baseline characteristics of studies in naïve comparison (1/2)

Baseline characteristics (Lifileucel: C-144-01, Chemotherapy: Mangin et al.)

Characteristic	C-144-01 Pooled Cohorts 2 and 4 ([redacted])	Mangin et al. (2021) ICI group (N=50)	Is a smaller treatment effect expected if adjusted?
Age, median (range)	[redacted]	68.25 (NR; SD:13.27)	**Yes** (the Mangin population appeared to be older)
Sex, n (%):			**Unknown**, likely small or no impact
Male	[redacted]	26 (52.0)	
Female	[redacted]	24 (48.0)	
Disease stage, n (%):			**Yes** (the Mangin population has a higher proportion of patients at late disease stage)
IIIC	[redacted]	-	
IV	[redacted]	-	
IIIcd/IV M1ab (if further specified)	[redacted]	7 (14.0)	
M1c (if further specified)	[redacted]	23 (46.0)	
M1d (if further specified)	[redacted]	20 (40.0)	
IV (no further specified)	[redacted]	-	
ECOG score, n (%):			**Yes** (the Mangin study has a higher proportion of patients with ECOG score of 2, [redacted])
0	[redacted]	16 (39.0)	
1	[redacted]		
≥2	[redacted]	25 (61.0)	

Baseline characteristics of studies in naïve comparison (2/2)

Baseline characteristics (Lifileucel: C-144-01, Chemotherapy: Mangin et al.)

Characteristic	C-144-01 Pooled Cohorts 2 and 4 ([redacted])	Mangin et al. (2021) ICI group (N=50)	Is a smaller treatment effect expected if adjusted?
LDH level (U/L), n (%):			**Yes** (the Mangin study has a higher proportion of patients with high LDH)
≤ULN/Normal	[redacted]	10 (23.8)	
>ULN	[redacted]	32 (76.2)	
Melanoma subtype, n (%)			**Unknown** (not enough data reported for the C-144-01 population)
Cutaneous	[redacted]	NR	
Mucosal	[redacted]	6 (12.0)	
Acral	[redacted]	6 (12.0)	
SSM	[redacted]	17 (34.0)	
Nodular	[redacted]	4 (8.0)	
BRAF status, n (%):			**Unknown**
Mutated	[redacted]	0 (0.0)	
Wild type	[redacted]	34 (68.0)	
Other	[redacted]	14 (28.0)	
Unknown	[redacted]	2 (4.0)	
Metastases, n (%)			**Yes** (the Mangin study has a higher proportion of patients with brain metastases)
Liver	[redacted]	NR	
Brain	[redacted]	32 (64.0)	
Time from last prior anti-PD-(L)1, median (range)	[redacted]	NR	

Unadjusted KM curves lifileucel v chemotherapy for PFS & OS

Figure: Unadjusted KM curves of PFS of lifileucel v chemotherapy

Figure: Unadjusted KM curves of OS of lifileucel v chemotherapy

Link to - Overview of company's model

Lifileucel treatment proportion receiving regimen

Patients flow between tumour harvest and receiving lifileucel infusion

Outcome	%	Assumptions
Died between tumour harvest and infusion	[redacted]	• Assigned only the costs associated with the surgical resection of tumour tissues and end-of-life care
Discontinued between tumour harvest and infusion	[redacted]	• Incur the costs of the tumour tissue procurement and [redacted] incur the costs of LD chemotherapy. Costs of the infusion and IL-2 therapy not incurred • Health outcomes and costs are assumed to be derived from a 'standard care' comparator based on a weighting of individual comparators (ipilimumab [redacted], chemotherapy [redacted], and BSC [redacted])
Received lifileucel infusion that is out-of-specification	[redacted]	• Incur the same costs as the group receiving the infusion within specification, except for the cost of the lifileucel infusion itself, which is assumed not to be paid for by the NHS. • Health outcomes and costs are assumed to be derived from a 'standard care' comparator
Received lifileucel infusion that met the SmPC specification*	[redacted]	• 100% incur costs of the tumour tissue procurement, 100% incur costs of LD chemotherapy, 100% incur costs of the lifileucel infusion and [redacted] incur the costs of IL-2 therapy. • Assigned the costs and outcomes associated with the lifileucel regimen.

Company: *"It is expected that the proportion of patients receiving lifileucel within the SmPC dosing range will increase over time as the manufacturing process continues to improve. Clinicians will gain more experience selecting appropriate and medically fit patients for lifileucel which, in turn, will reduce the discontinuation rates between tumour harvest and actual lifileucel infusion. Additionally, lifileucel will only be manufactured in facilities approved for commercial manufacturing, the number of which will increase over time. Therefore, the discontinuation rates above were assumed to be representative of the discontinuation expected in clinical practice at launch, however it is expected that discontinuation will decrease over time"*

Link to - Survival models ipilimumab

Studies identified by the company (1/2)

Table: Ipilimumab as a further line of treatment in melanoma literature

Publication	Company description / observation
Patrinely et al. (2020)	A RWE study on the outcomes of metastatic melanoma patients treated with anti PD-1 after disease progression, reported a complete and partial response of 0% for those treated with ipilimumab after disease progression which did not indicate long-term survival in patients
Long et al. (2022)	Reported that among 103 treatment-naïve patients with unresectable stage III/IV melanoma who received pembrolizumab followed by ipilimumab, six patients remained alive at 40 months, with one patient remaining alive at 45 months
Cybulska-Stopa et al. (2020)	Reported that ipilimumab administered after PD-1 therapy resulted in a 2-year survival rate of 3%
Wilson et al. (2021)	A study on sequential immunotherapy in metastatic melanoma based on a small number of patients, reported that 0% of patients treated with ipilimumab as 2L treatment achieved PFS at 12 months with the median OS of 3.4 months. The study concluded that "*ipilimumab is not efficacious in patients who progress after anti-PD-1 agents*".

Link to - outcomes for cured patients

Studies identified by the company (2/2)

Table: Outcomes for long-term survivors literature

Publication	Company description / observation
Sadeq et al. (2023)	A retrospective observational study on the US population used the SEER database to determine the SMR of melanoma patients. This study found no difference in risk of death between melanoma survivors and the general population, indicating an SMR of 1 was most appropriate for melanoma patients.
Seitter et al. (2021)	Found that the melanoma-specific survival of responders receiving TIL in metastatic melanoma (regardless of whether they received prior PD-1 treatment) did not show any decrease after 36 months, indicating that there were no deaths due to melanoma; therefore a SMR of 1 was suitable
Wolchok et al. (2024)	A randomised trial assessing the long-term outcomes of first line metastatic melanoma patients, found that the OS of patients treated with either ipilimumab+nivolumab, nivolumab or ipilimumab started to stabilise around 66 months, indicating that they were following mortality akin to the general population.

Link to - Utility values

Utility values

Table: Summary of health state utility values for cost-effectiveness analysis (Base case and scenarios)

		Company			EAG	
Health state	**Company/ EAG base case**	**non-EQ-5D values Excluded***	**Retel et al****	**TA357**	**TA268, TA321, TA562*****	**Lifileucel administration disutility doubled**
Progression free (PF)	0.77	0.76	0.85	0.74	0.8	-
Progressed disease (PD)	0.67	0.70	0.59	0.69	0.68	-
Disutility associated with the lifileucel administration	0.09	0.09	0.09	0.09	0.09	0.18

*Retel et al., TA269 ,TA319 **Largest difference between the PF and PD values ***Reflects a larger difference in utility values between the health states compared with the company's base case analysis

Components of CAR-T tariff

Link to - Set-up, logistics, training and delivery costs (2/2)

Costs associated with	Covered by tariff?	Relevant for CAR-T?	Relevant for lifileucel?	To be covered separately to tariff in model?
Leukapheresis	Yes	Yes	No	No*
Therapy delivery in hospital	Yes	Yes	Yes	No
Adverse events in hospital	Yes	Yes	Yes	No*
Monitoring for 100 days	Yes	Yes	Yes	No
Training	Yes	Yes	Yes	No
Collection of cancer tissue	No	No	Yes	No*
Interleukin-2 administration + subsequent inpatient care	No	No	Yes	No*
Conditioning and bridging chemo acquisition, administration and delivery (aka lymphodepletion)	No	Yes	Yes	Yes
Product acquisition	No	Yes	Yes	Yes
Subsequent treatments	No	Yes	Yes	Yes
Subsequent allo-SCT	No	Yes	No	No

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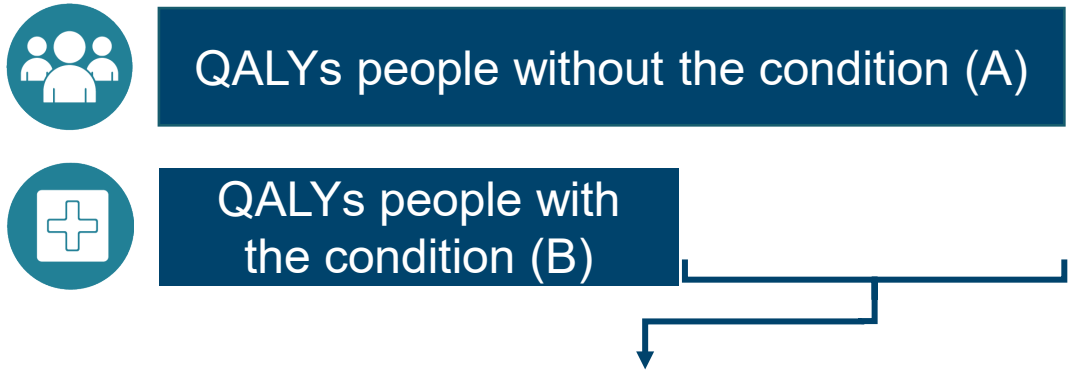
*Costs of collection of cancer tissue and interleukin-2 not included in tariff offset by costs of leukapheresis and higher expected AEs with CAR-T included in tariff

Abbreviations: AE, Adverse event; Allo-SCT, allogeneic stem cell transplant; CAR-T, Chimeric antigen receptor T-cell;

QALY weightings for severity

Severity modifier calculations and components:



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

Abbreviations: QALY, quality-adjusted life year

Outcomes for people who do not receive lifileucel

EAG no longer considers uncertainty around outcomes for patients who do not receive the lifileucel infusion to be a key issue

Background

- Model assumes that [redacted] of people that are eligible for lifileucel do not receive it ([redacted] discontinue between tumour harvest and infusion and [redacted] receive a lifileucel infusion that is out-of-specification)
  - ↳ Health outcomes derived from a 'standard care' comparator based on a weighting of individual comparators (ipilimumab [redacted], chemotherapy [redacted], and BSC [redacted])

EAG comments:

- Initially unsure if the modelled outcomes for people who do not receive lifileucel infusion reflect what was observed in Study C-144-01
- PFS and OS KM plots for people who underwent tumour harvesting but did not receive the infusion in Study C-144-01 were provided post clarification and broadly support the company's assumption
- PFS and OS KM used to estimate RMST → Estimated RMST lower than modelled mean OS and PFS using EAG preferred assumptions (RMST standard errors large and likely underestimates overall mean OS time because some people remained alive at the end of follow-up)
- Scenario analysis performed where the estimated mean PFS and OS of people that do not receive lifileucel was shrunk → Analysis only had a small impact on the cost effectiveness estimates

Abbreviations: BSC, Best supportive care; EAG, External Assessment Group; KM, Kaplan-Meier; OS, Overall survival; PFS, Progression-free survival; RMST, Restricted mean survival time;

Outcomes for people who do not receive lifileucel (2/2)

Comparison of mean PFS and OS – non-infused patients in Study C144-01 and EAG-preferred assumptions

Outcome	PFS (Years)	OS (Years)
Model - weighted estimate of BSC, chemotherapy and ipilimumab	[redacted]	[redacted]
Study C-144-01 – RMST	[redacted]	[redacted]

EAG preferred and additional analyses results – lifileucel versus ipilimumab, chemotherapy and BSC, pairwise comparisons

Technology	LYGs	QALYs	Costs	Inc. LYG	Inc. QALYS	Inc Costs	ICER (excl. SM)	ICER (incl. SM)
EAG-preferred analysis (DM=1.2)								
Lifileucel	5.15	2.67	[redacted]	-	-	-	-	-
Ipilumumab	1.50	0.88	[redacted]	3.65	1.79	[redacted]	[redacted]	[redacted]
Chemotherapy	0.79	0.56	[redacted]	4.35	2.11	[redacted]	[redacted]	[redacted]
BSC	0.79	0.56	[redacted]	4.35	2.11	[redacted]	[redacted]	[redacted]
EAG-preferred analysis + PFS and OS for lifileucel non-infused patients in Study C144-01 (SM=1.2)								
Lifileucel	5.10	2.64	[redacted]	-	-	-	-	-
Ipilumumab	1.50	0.88	[redacted]	3.60	1.76	[redacted]	[redacted]	[redacted]
Chemotherapy	0.79	0.56	[redacted]	4.30	2.08	[redacted]	[redacted]	[redacted]
BSC	0.79	0.56	[redacted]	4.30	2.08	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, Best supportive care; EAG, External Assessment Group; ICER, Incremental cost-effectiveness ratio; Inc, Incremental; LYG, Life year gained; OS, Overall survival; PFS, Progression-free survival; QALY, Quality-adjusted life year; RMST, restricted mean survival time; SM, Severity modifier

See appendix – Relevant sections from the NICE methods manual

Discount rate

Company: 1.5% discount rate may be appropriate – presented in scenario analyses

Company

Base case 3.5% discount rate applied to both costs and outcomes (scenario 1.5% discount rate)

- Lifileucel meets all 3 requirements listed in the NICE methods manual
  - ↳ RWE shows low HRQoL and median OS between 4 and 12.3 months at 2L or later
  - ↳ C-144-01 supports a curative effect and ability to restore health in a significant proportion of people
  - ↳ In C-144-01 21.9% survived ≥4 years, highlighting the potential of lifileucel to extend survival

EAG comments

Base case 3.5% discount rate applied to both costs and outcomes (scenario 1.5% discount rate)

- A minority of people eligible for lifileucel are expected to experience long term OS and HRQoL benefits
- The model predicts approximately [redacted] of people in whom lifileucel treatment is planned will achieve cure, and the remaining [redacted] will have poor survival outcomes
  - ↳ Model assumes 70% of people will receive the infusion, and of these, the company's base case applies an estimated cure fraction for OS of [redacted] (unadjusted MCM)

Abbreviations: 2L, Second line; HRQoL, Health-related quality of life; MCM, Mixture-cure model; OS, Overall survival; RWE, Real world evidence;

Link to – Discount rate

Relevant sections from the NICE methods manual

Background

- NICE methods manual (section 4.5.3): *"committee may consider analyses using a non-reference-case discount rate of 1.5% per year for both costs and health effects, if, in the committee's considerations, all of the following criteria are met:*
  - *The technology is for people who would otherwise die or have a very severely impaired life.*
  - *It is likely to restore them to full or near-full health.*
  - *The benefits are likely to be sustained over a very long period."*
- NICE methods manual (section 4.5.4): *"When considering analyses using a 1.5% discount rate, the committee must take account of plausible long-term health benefits in its discussions. The committee will need to be confident that there is a highly plausible case for the maintenance of benefits over time when using a 1.5% discount rate."*
- NICE methods manual (section 4.5.5): *"…committee will need to be satisfied that any irrecoverable costs associated with the technology (including, for example, its acquisition costs and any associated service design or delivery costs) have been appropriately captured in the economic model or mitigated through commercial arrangements.*

Should analyses using a non-reference-case discount rate of 1.5% per year for both costs and health effects be considered?