Single Technology Appraisal

Lifileucel for previously treated unresectable or metastatic melanoma [ID3863]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Lifileucel for previously treated unresectable or metastatic melanoma [ID3863]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Iovance Biotherapeutics:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Expert perspectives** from:
   a. Prof. James Larkin – Clinical expert, nominated by Iovance Biotherapeutics, Inc
   b. Heather Shaw – Clinical expert, nominated by Melanoma Focus
   c. Susanna Daniels – Patient expert, nominated by Melanoma Focus
   d. Jane Henderson – Patient expert, nominated by Melanoma Focus

4. **External Assessment Report** prepared by School of Health and Related Research (ScHARR)
   a. EAG addendum

5. **External Assessment Report – factual accuracy check**
   a. EAG addendum factual accuracy check

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Lifileucel for previously treated unresectable or metastatic melanoma [ID3863]

Company evidence submission

March 2025

File name	Version	Contains confidential information	Date
ID3863_Lifileucel in unresectable melanoma_CS_1.0_FINAL	**1.0**	**Yes**	**13 March 2025**

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1 Decision problem, description of the technology and clinical care pathway

1.1 Decision problem

The objective of this single technology appraisal (STA) is to evaluate the clinical and cost-effectiveness of lifileucel (brand name AMTAGVI®) for the treatment of adult patients with unresectable or metastatic melanoma. The marketing authorisation for lifileucel is being reviewed by the Medicines and Healthcare products Regulatory Agency (MHRA) and target date for the regulatory approval is May 2025. The anticipated market authorisation for lifileucel is: "[redacted]

The decision problem that this submission addresses is presented in Table 1 below, which aligns with the National Institute for Health and Care Excellence (NICE) final scope for this appraisal.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with previously treated unresectable or metastatic melanoma	[redacted]	Aligned with SmPC
Intervention	Lifileucel	In line with scope	N/A
Comparator(s)	Ipilimumab monotherapy Dacarbazine Temozolomide Paclitaxel Paclitaxel and carboplatin Best supportive care	Chemotherapy comparators including those listed in the final scope, were grouped into one comparator arm.	Individual product data for chemotherapy in melanoma is not available, therefore, existing pooled data across chemotherapy regimens sourced from the literature was leveraged as a proxy. Clinical expert validation confirmed this approach is appropriate, with no difference in outcomes.
Outcomes	Progression-free survival Overall survival Response rates Safety Health-related quality of life	In line with scope	N/A
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.	As per final scope issued by NICE: A cost-effectiveness analysis will be performed, expressed in terms of incremental cost per QALYs.	N/A

	The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to capture the costs and health outcomes of potential long-term survivors and to reflect most of the differences in costs or health outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be considered.	A lifetime time horizon of 45 years is used in the base case analysis. Costs will be considered from an NHS and PSS perspective. A simple patient access scheme (PAS) is considered for the intervention. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be considered. Cost-effectiveness analysis in the proposed population is presented comparing lifileucel with ipilimumab, chemotherapy and best-supportive care. For further details please refer to Section B.3	

Abbreviations: MEK, Mitogen-activated protein kinase; N/A, Not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PD-1, Programmed Death-1; PSS, Personal Social Services; QALY, Quality-adjusted life year' SmPC, Summary of Product Characteristics.

1.2 Description of the technology being evaluated

Table 2 summarises the technology being evaluated in this submission. The current summary of product characteristics (SmPC) and the European Public Assessment Report (EPAR) are provided in Appendix A.

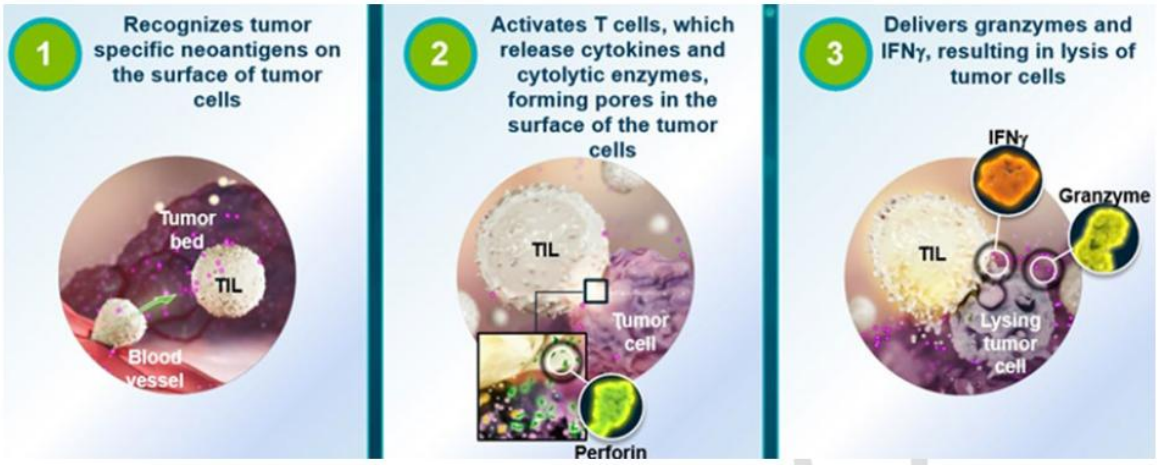
Table 2: Technology being evaluated

UK approved name	Lifileucel
Brand name	AMTAGVI®
Mechanism of action	Lifileucel (AMTAGVI®) is a one-time treatment with a novel mechanism of action that is distinct from immune checkpoint blockade therapies.[1] Lifileucel is primarily composed of tumour-derived CD4+ and CD8+ T-cells, which are recovered from patient's tumor-tissues and mostly of effector-memory phenotype associated with cytotoxic function.[2] In the proposed mechanism of action of lifileucel, tumour-derived T-cells enter the tumour microenvironment and mediate tumour cell death through release of cytokines and cytolytic enzymes, promoting cell lysis.
Marketing authorisation/CE mark status	The anticipated market authorisation is: [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	N/A
Method of administration and dosage	Lifileucel is administered in an inpatient hospital setting under the supervision of a physician experienced in the use of anticancer agents. An intensive care facility and specialists skilled in cardiopulmonary or intensive care medicine must be available.[1] Lifileucel is supplied in 1 to 4 patient-specific infusion bag(s) in individual protective metal cassettes. The product is thawed prior to administration back into the same patient. Surgical resection: A melanoma lesion is surgically removed and then shipped in a hypothermosol solution to the manufacturing site. The manufacturing process takes around 22 days. An additional 10 days are needed for product quality testing after which the product is shipped back to the site as a cryopreserved product. Therefore, from the surgery until infusion of lifileucel back to patients, the total turnaround time is ~33 days.

	Lifileucel is administered in a 3-step procedure with approximately an 11-day duration: • Lymphodepletion: the patient receives lymphodepleting chemotherapy regimen in preparation of receiving lifileucel, to remove any negative inhibitory or regulatory cells in the tumour microenvironment (Day -7 to Day-1). • Lifileucel infusion: Lifileucel is infused as within 24 to 96 hours after the last dose of chemotherapy.[3] • Beginning 3-24 hours after lifileucel infusion, IL-2 is administered every 8-12 hours for up to a maximum of 6 doses to support cell expansion *in vivo* (Day 0 up to Day 4) (Figure 2). IL-2 infusion requires a period of monitoring in a hospital setting for patients.
Additional tests or investigations	No additional tests or investigations are required.
List price of treatment	[redacted]
Patient access scheme (if applicable)	A simple PAS discount of [redacted] will be applied to the list price of lifileucel, resulting in a net price of [redacted]

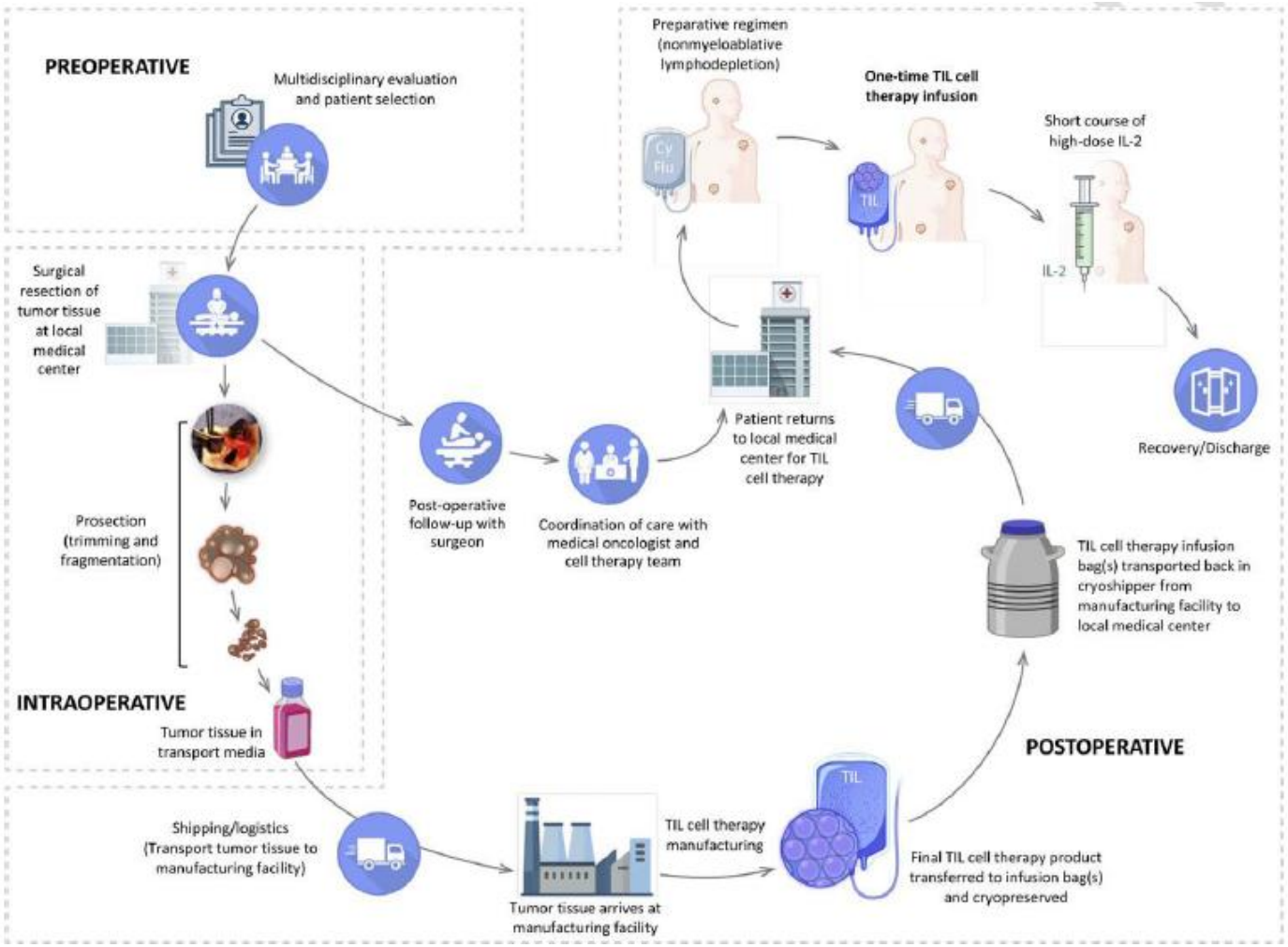
Abbreviations: CD4+, Cluster of Differentiation 4 positive; CD8+, Cluster of Differentiation 8 positive; CHMP, Committee for Medicinal Products; FDA Food and Drug Administration; IL-2, Interleukin 2; IV, Intravenous; MEK, Mitogen-activated protein kinase; MHRA, Medicines and Healthcare products Regulatory Agency; PD-1, Programmed Death-1; TIL, Tumour-Infiltrating Lymphocytes.

Figure 1: Proposed mechanism of action



Abbreviations: IFN, interferon; TIL, tumour-infiltrating lymphocytes.
Source: Zamora (2018)[4], Chavez-Galan (2009)[5], Rosenberg (2011)[6], Human (2021)[7]

Figure 2: Steps and timelines for the administration of lifileucel T cell therapy (total ~33 days)



Abbreviations: TIL, tumour-infiltrating lymphocytes.
Source: Mullinax (2022)[8]

The patient-specific, single-dose nature of treatment with lifileucel represents a significant divergence in the treatment paradigm of this aggressive disease, offering a new treatment modality with the potential for deep and durable responses, and sustained long-term survival for these patients, as well as a substantial reduction in patient burden during treatment.

1.3 Health condition and position of the technology in the treatment pathway

1.3.1 Disease overview

Melanoma is a disease that arises when abnormal melanocyte skin cells begin to uncontrollably grow and divide, forming tumours.[9] The timely diagnosis of melanoma is essential to allow for efficient intervention and management of the disease. Stage I-IIIb melanoma is less challenging to treat compared to advanced melanoma, due to localisation of the cancer, and can often be cured through surgery alone.[10,11] However, if the disease has progressed to unresectable or distant metastatic (Stage IIIc and beyond), treatment becomes much more challenging and ultimately results in lower survival rates.[12] Therefore, early diagnosis is essential to prolong patient survival, alleviate the symptoms of the disease and decrease the impact of the disease on patient's and carer's quality of life (QoL).

1.3.2 Staging

Key prognostic factors in melanoma include thickness and/or level of invasion of the lesion, mitotic index, ulceration or bleeding from the primary lesion, number of regional lymph nodes involved, and systemic metastases.[13] These prognostic factors are included in The American Joint Committee on Cancer (AJCC) staging system, (9th version) currently used in UK guidelines.[13] The AJCC system uses the tumour, node, metastasis (TNM) method while considering additional prognostic characteristics of the tumour such as thickness, presence of ulceration, and the presence of mitosis in lesions <1 mm in thickness:

- Tumour (T) – designates the size and invasiveness of the primary tumour.

- Nodes (N) – identifies the presence or absence of tumour in the regional lymph nodes.

- Metastases (M) – identifies the presence or absence of distant metastases, including non-regional lymph nodes.

Using the information from TNM classification, melanoma is further grouped into clinical prognostic stages, which can also inform general five-year survival rates. Since this submission is focused on the metastatic/unresectable setting, Appendix M presents TNM classification of Stages III-IV of the disease and corresponding 5-year survival rates.[12,13]

1.3.3 Diagnosis of disease

Staging and risk assessment procedures are determined by disease presentation at diagnosis. Abnormal pigmented lesions are clinically analysed using the European Society for Medical Oncology (ESMO) guidelines, which recommends the 'ABCD' rule, assessing **A**symmetry, **B**order irregularities, **C**olour heterogeneity and **D**ynamics (evolution in colours, elevation or size).[14] Dermoscopy and full body imaging may also be performed by an experienced physician to enhance diagnostic accuracy and early detection.[14]

Appropriate surgical management is also critical for diagnosis and staging of melanoma, with the goals of surgery including histologic confirmation, accurate micro-staging and appropriate excision of the margin around the primary site.

If metastatic disease is suspected at diagnosis, a comprehensive staging protocol is initiated, including whole-body computed tomography (CT), positron emission tomography (PET), PET/CT, magnetic resonance imaging (MRI) of the brain and evaluation of serum lactate dehydrogenase (LDH) levels. Classification of Eastern Cooperative Oncology Group (ECOG) performance status is also obtained, to assess the extent of disease, evaluate the presence of brain metastases and assess key prognostic markers of metastasis, respectively.[15]

According to UK clinical experts in attendance at a clinical advisory board conducted by the Company in October 2024, for patients with metastatic melanoma, BRAF and

MEK status is routinely tested to determine if the patient is eligible for targeted therapy.[16] However, clinicians do not routinely perform tumour PD-L1 biomarker tests on patients in UK clinical practice, as approved melanoma treatments do not have a PD-L1 companion diagnostic test requirement.[16]

1.3.4 Epidemiology

Melanoma is the fifth most common cancer worldwide and the third most common cancer in individuals aged 15–29, with global incidence rates increased by 182.3% from 1990 to 2021.[17] In the UK alone, incidence rates for melanoma have risen by 147% since 1993, representing a substantial threat to population health and QoL .[18–21] Unlike many other cancers, melanoma disproportionately affects the younger population; it is the third most common cancer among 15-39 year olds in the UK and around 50% of people diagnosed are under 65 years old.[22,23] This highlights the societal burden of melanoma through its' impact on workforce productivity, economic costs, and the added caregiving responsibilities often faced by families with young dependents.[21,24] These factors emphasise the broad implications of metastatic melanoma on public health and society.

Melanoma is an aggressive disease with a high risk for mortality if not treated in a timely manner.[25,26] Melanoma deaths have increased by 86.1% from 1990 to 2021.[17] According to Cancer Research UK, melanoma was responsible for 2,314 deaths per year between 2017-2019 and, despite the recent advances in the metastatic treatment setting, the prognosis for unresectable or metastatic melanoma remains poor.[24] According to the National Disease Registration Service, over a third (35.3%) of melanoma cases are diagnosed at Stage I. Although a smaller percentage of melanoma patients are diagnosed at Stages III (16.1%) and IV (10.2%), these stages account for a high number of melanoma-related deaths.[21,27] While patients with Stage IIIc disease have a 5-year survival rate of 69%, this rate reduces to just 32% for Stage IIId disease, and 22.5% for Stage IV.[28]

In line with the anticipated marketing authorisation of lifileucel, Stage IIIc, IIId and IV melanoma will be the focus of this submission.

1.3.5 Risk factors

There are many risk factors associated with melanoma, as detailed in Table 3.

Table 3: Risk factors for the development of melanoma

Non-modifiable risk factors	Modifiable risk factors
Family history of melanoma Fair skin Blonde or red hair Multiple nevi and/or dysplastic nevi History of non-melanoma skin cancer Chronic immunosuppression Age >65 years Male sex (with increasing age)	Exposure to ultraviolet rays (including sun exposure and indoor tanning) Sunburn

Source: Cancer Research UK (2024)[24]

Ultraviolet (UV) exposure is responsible for around 85% of melanoma cases caused by intermittent sun exposure, sunburn, sunbeds and lack of sun protection when out in the sun.[24] This is primarily attributed to the association between UV exposure and resulting DNA damage causing high rates of mutations per megabase.[29] Melanoma is also associated with non-modifiable factors such as gender, age and inherited mutations.[27]

In addition to inherited mutations, there are also key acquired mutations that can result in melanoma. BRAF are the most frequently mutated oncogenes in melanoma, with around 50% of all melanomas containing BRAF mutations.[30,31] The most frequent of these is a single point mutation at codon 600 (V600E) which leads to the constitutive activation of the BRAF signalling pathway.[31] Due to the mutation's prevalence within melanoma patients, it has been an area of great interest for the development of targeted systemic therapies.

1.3.6 Symptoms

Early-stage melanoma can be largely asymptomatic, with initial symptoms including a mole that changes size, shape or colour over time, which often goes unnoticed in addition to general unexplained weight loss, fatigue and pain which are burdensome but are not specific to melanoma and therefore may be overlooked.[32] If the melanoma is localised and detected early this can usually be efficiently treated

through surgical resection with or without adjuvant targeted therapy or adjuvant immunotherapy.[11,14,33–37] Only once the melanoma has metastasised a diverse range of severe symptoms in the lungs, liver, bone or brain can occur depending on where the metastatic tumour grows:[38,39]

- **Lungs** – Coughing (with or without blood), chest pain, shortness of breath, fluid around the lungs.
- **Brain** – Headache, paralysis in the arms or legs, sleepiness, difficulty with memory, behavioural changes, difficulties with hearing, sight or swallowing, seizures and nausea.
- **Bones** – Aching, back pain, numbness, brittle bones, changes in calcium levels.
- **Liver** – Loss of appetite, fatigue, jaundice, swelling in the abdomen and legs, itchiness.

1.3.7 Burden of unresectable or metastatic melanoma

1.3.7.1 Patient quality of life burden

The Global Burden of Disease (2021) study assessed the worldwide impact of melanoma, including all stages, by measuring disability-adjusted life years (DALYs).[17] One DALY represents the loss of one year of healthy life due to illness, disability, or premature death. The study found that melanoma ranks eighth among all diseases in terms of age-standardised DALY rates; the total DALYs attributed to melanoma globally in 2021 were approximately 6.18 million, reflecting a 63.7% increase since 1990.[17,40] Alzheimer's disease, by comparison, is attributed to approximately 7,44 million DALYs worldwide, highlighting the significant burden of melanoma. This substantial DALY rate highlights the considerable morbidity burden imposed on melanoma patients across all disease stages over the past three decades, reflecting the long-term health impact and quality-of-life reductions associated with the disease.

The substantial symptom burden of metastatic melanoma has widespread impacts on patient QoL, with patients with metastatic (Stage III/IV) melanoma often reporting that they are affected by sleep problems, primarily due to anxiety, stress, and/or worry related to their condition, pain, or discomfort.[41] A total of 16 published studies that assessed health-related quality of life (HRQoL) using the Functional Assessment of Cancer Therapy-Melanoma (FACT-M) questionnaire were summarised in a systematic literature review conducted by Bagge *et al.* (2022).[42] The FACT-M scores were reported by stage of disease, and illustrated that as the stage of disease increased FACT-M scores decreased. FACT-M scores, which range from 0 to 172, decreased overall, with lower scores indicating a decreased HRQoL. This deterioration in HRQoL is seen in all individual categories apart from social wellbeing, which has been attributed to increasing social support as patients become more physically burdened. These results are summarised in Table 4.

Table 4: FACT-M mean scores based on AJCC stage of disease

Mean Score	Stage I/II	Stage III	Stage IV
FACT-M	**152.8**	**134.7**	**130.2**
Social wellbeing	22.9	23.3	25.0
Emotional wellbeing	19.4	19.1	18.6
Physical wellbeing	24.7	24.1	23.2
Functional wellbeing	22.1	22.0	21.7

Notes: FACT-M is derived from the generic Functional Assessment of Cancer Therapy-General (FACT-G), published by FACIT.[43] FACT-G comprises 27 items that are divided into four sections, each with seven items: Physical Well-Being (PWB); Social and family Well-Being (SWB); Emotional Well-Being (EWB) and Functional Well-Being (FWB). Each item refers to HRQoL within the past week and are rated from 0 'not at all' to 4 'very much', with a total score ranging from 0-108, with a higher score indicating better quality of life. The FACT-M consists of 51 items: 27 items comprising the FACT-G subscale; 16-item Melanoma Subscale (MS, total score ranging from 0 to 64) and 8-item Melanoma Surgery Scale (MSS, ranging from 0 to 32).
Abbreviations: AJCC, American Joint Committee on cancer; FACT-M, Functional Assessment of Cancer Therapy-Melanoma.
Source: Bagge *et al.* (2022)[42]

HRQoL decreases as the severity of melanoma increases, likely due to multiple factors, including disease-related symptoms (discussed in Section 1.3.6) as well as substantial short-term and long-term adverse events (AEs) associated with systemic treatment such as rash, pruritus, fatigue and arthralgia, which can cause a substantial physical burden.[44–46] According to UK clinical experts, patient HRQoL trajectory can vary. Some patients experience a steady decline as the disease progresses, whilst other individuals often with better baseline health status may

experience a slower rate of decline, followed by a more rapid deterioration in QoL as they approach end of life.[16]

Emotional wellbeing of patients with unresectable, metastatic melanoma is also substantially impacted. Individual interviews conducted by Cheung *et al.* (2018) indicated 48% of patients with advanced melanoma reported their sense of self had altered and were struggling with self-identity.[41] Furthermore, a study conducted by Beutel *et al.* (2015) assessed melanoma patients through the use of the Patient Health Questionnaire-9 (PHQ-9) scale, which uses a nine-item questionnaire to rate each QoL item on a four-point scale (zero indicates no effect and four represents a considerable impact of everyday life). Patients reported substantially increased depression and fear of recurrence, stating an average PHQ-9 score of 3.87 compared to 2.38 for the general population.[47]

1.3.7.2 Caregiver burden

As the number of melanoma patients continue to rise, so does the number of people who are caring for patients with melanoma.[48] Macmillan Cancer Support UK estimates that around 1.5 million people are caring for someone with cancer, spending an average of 17.5 hours a week looking after them.[48] This represents a substantial burden to caregiver's QoL, affecting them both physically and mentally. During providing care to a melanoma patient, 20-35% of carers experience one or more issues with their own physical health, including exhaustion, insomnia and weight gain. Furthermore, up to 70% of carers experience issues with their mental health, primarily related to disrupted schedules, financial problems and emotional stress.[49] Thompson *et al.* (2023) assessed the QoL of 120 caregivers through a quantitative cross-sectional survey using Supportive Care Needs Survey – Partners and Caregivers module (SCNS-P&C). In this survey, over one third (33%) of caregivers, regardless of the patient's disease stage, reported at least one unmet need where the highest unmet need was in the psychological/emotional domain and 35% of caregivers were using a psychologist for support.[50] Finally, 25% of caregivers reported high levels of financial burden, primarily due to employment breaks including time off or taking a leave of absence, as well as out-of-pocket costs.[51]

1.3.7.3 Economic and socioeconomic burden

The cost of managing patients with melanoma increases as the disease progresses, with metastatic melanoma representing a substantial burden to the healthcare system [52,53] This increase is largely driven by the use of novel and increasingly more expensive therapies (discussed in Section 1.3.8), along with higher rates of disease- and treatment-related adverse events (TRAEs), leading to higher health care resource use and the associated costs.[53]

According to the Jayathilaka *et al.* (2024) study, the mean event rate for six types of TRAEs is 30.0% for melanoma patients receiving either immune checkpoint inhibitor (ICI) monotherapy or ICI combination therapy.[54] Given this high incidence, the resource burden of adverse event management for immunotherapy is substantial, with annual costs estimated to be £2,835-£2,860 per patient.[55]

Complex surgical resections, palliative care, and administration of chemotherapy also incur high direct costs.[56] A study on the economic impact of healthcare resource use patterns among patients with unresectable Stage III-IV melanoma found that annual hospitalisation costs were £3,225 per patients, largely due to toxicity during systemic therapy and disease progression during supportive care.[56]

In addition, the resource use of patients receiving nivolumab plus ipilimumab as first line of treatment (LoT; introduced in Section 1.3.8.1), which was calculated in 2019, was approximately £226K annually. This annual cost was taking into account drug costs, hospitalisations, procedures and surgeries associated with the management of metastatic melanoma.[57]

Furthermore, given that 50% of unresectable or metastatic melanoma patients are under 65 years of age, the high mortality and morbidity associated with the disease results in a loss of economic productivity and presents a sizeable economic burden.[58] In the UK, an estimated 9,555 years of productivity are lost annually due to melanoma across the entire population.[59] This socioeconomic burden grows drastically with the progression of melanoma, due to treatment options often being intensive and time consuming. A survey of healthcare professionals and patients, conducted by Aguiar-Ibanez *et al.* (2023)[60], reported that 20% of patients receiving a

bi-weekly infusion of nivolumab missed an average of 230 minutes of paid work, 145 minutes of household chores, and 149 minutes of leisure on the day of infusion.[60] Moreover, 20% of patients reported having an unpaid caregiver who themselves missed an average of 270 minutes of paid work in between the days before and after infusion.[60]

1.3.8 Current treatment options

1.3.8.1 UK clinical guidelines

There are several treatment options available to patients with unresectable or metastatic melanoma which aim to improve QoL and prolong patient survival.[61] These include immunotherapy via ICIs, targeted therapy using signal transduction inhibitors, chemotherapy, and best supportive care (BSC).[62] The use of ICIs, such as pembrolizumab and nivolumab (anti-PD-1 antibodies), has led to a considerable improvement in patient outcomes for Stage IIIc-IV melanoma.[63]

The guidelines used in the UK for the treatment of unresectable or metastatic melanoma are the NICE melanoma assessment and management guidelines (NG14, 2022).[10] The first-line treatment options recommended for unresectable or metastatic melanoma are combination immunotherapy and targeted therapy agents. The guidelines state that clinicians should consider the individual clinical characteristics of each patient to assess the most appropriate treatment, including but not limited to:

- Comorbidities
- Risk of treatment toxicity
- Patient tolerance of treatment toxicity
- Presence of brain metastases
- Tumour characteristics e.g. LDH levels
- Timing of progression

According to this guideline, the first-line treatment recommended for patients with untreated unresectable or metastatic melanoma is nivolumab plus ipilimumab (an

anti–cytotoxic T-lymphocyte antigen-4 [CTLA-4] antibody), with pembrolizumab or nivolumab monotherapy as an alternative if the former is unsuitable or unacceptable.[10] Additionally, relatlimab in combination with nivolumab, has recently received approval from NICE as an alternative first-line treatment for untreated advanced (unresectable or metastatic) melanoma in people 12 years and older.[64]

Clinical experts at a UK clinical advisory board (October 2024) stated that treatment with ICIs is the preferred first-line option, regardless of BRAF status.[16] However, in the event of rapid disease progression or when immunotherapy is contraindicated or unsuitable, the next LoT recommended is largely dependent on patient BRAF status, with targeted BRAF kinase inhibitors, such as vemurafenib and dabrafenib, recommended for BRAF V600 mutation-positive patients.[10] These inhibitors can also be used in combination with MEK inhibitors, such as trametinib and binimetinib, simultaneously targeting the mitogen-activated protein kinase (MAPK) pathway in tumour cells.[31]

If patients haven't received an anti-PD-1 treatment at first-line, the aforementioned treatments are available as a second-line option. However, if patients have already received an anti-PD-1 treatment and a BRAF/MEK inhibitor (where appropriate), the remaining options are rather limited and include ipilimumab (if patients haven't received it as part of nivolumab plus ipilimumab combination as a first-line treatment), chemotherapy, BSC (including symptom management and palliative care) or entry into a clinical trial. UK clinical expert feedback at an advisory board in October 2024 stated clinicians refer between 20-50% of patients to clinical trials, prioritising this option to current ipilimumab, chemotherapy or BSC.

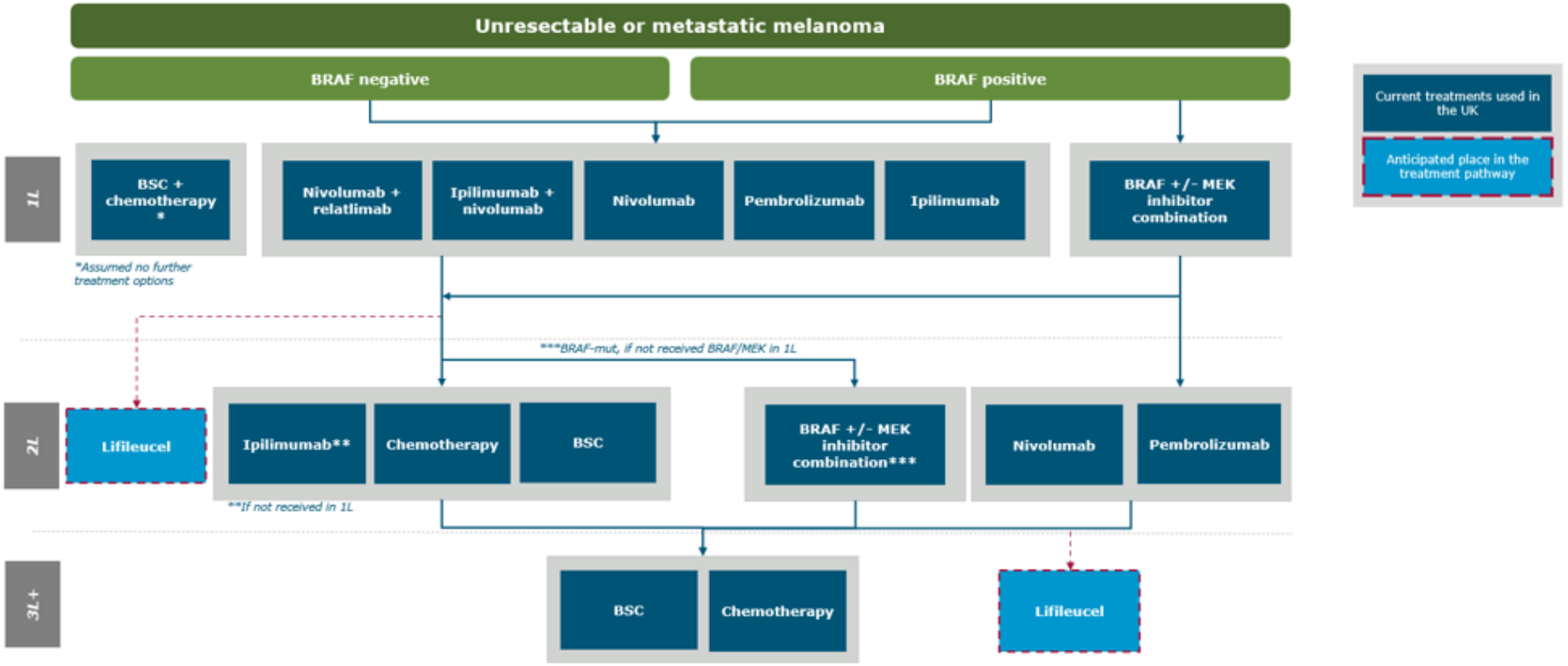
ESMO, the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) have also published guidelines for the management of unresectable or metastatic melanoma. These all highlight the importance of personalised treatment based on disease staging, BRAF mutation status, and PD-L1 expression. These guidelines consistently recommend immunotherapy as a first-line treatment where clinically possible, prioritising the combination therapy with nivolumab plus ipilimumab for advanced disease.[11,65] BRAF and MEK inhibitor combination therapy is recommended for BRAF-mutation

positive patients with rapidly progressing disease or contraindications for immunotherapy.[66] However, only one line of anti-PD-1 treatment, and only one line of BRAF inhibitors (for BRAF mutation positive patients only, with or without MEK inhibitors) are reimbursed by the National Health Service (NHS) implying retreatment with these agents is not an option in England and Wales, thereby limiting the list of effective treatment options that may improve outcomes at second-line treatment setting and beyond.[67]

All guidelines recommend BSC and chemotherapy with cytotoxic drugs, such as dacarbazine or temozolomide, as a last-line option for patients who have no further treatment options available due to its poor effectiveness with limited or no impact on survival outcomes in advanced melanoma.[10,11,65,66]

Figure 3 illustrates the current UK treatment pathway and treatment options for patients with unresectable or metastatic melanoma alongside the proposed positioning of lifileucel. Lifileucel is anticipated to be used as a second-line option for BRAF negative (wild type) patients, and as a third-line option for BRAF positive patients.

Figure 3. Current UK treatment pathway for patients with unresectable or metastatic melanoma and the proposed positioning of lifileucel within the pathway



†Patients will be eligible for lifileucel only if they received anti-PD-1 treatment (nivolumab or pembrolizumab) in 1L for BRAF negative pathway. For BRAF positive pathway, patients will be eligible for lifileucel only if they received anti-PD-1 therapy and a BRAF inhibitor in 1L or 2L.
Abbreviations: BSC, best supportive care; ESMO, European Society for Medical Oncology; MEK, mitogen-activated extracellular signal-regulated kinase; NICE, National Institute for Health and Care Excellence; 1L, first line; 2L, second line; 3L, third line.
Source: ESMO (2019)[14], NICE NG14 (2015)[10], TA269[68], TA321[69], TA357[70], TA366[71], TA544[72], TA400[73], TA950[64], TA319[74] TA562[75], TA396[76]

1.3.8.2 Previous NICE TAs in unresectable or metastatic melanoma

NICE recommends a range of treatments for unresectable or metastatic melanoma, including targeted therapies (e.g., dabrafenib, vemurafenib, trametinib with dabrafenib, and encorafenib with binimetinib) for BRAF V600 mutation-positive melanoma.[68,69,75,76] Immunotherapies (e.g., ipilimumab, pembrolizumab, nivolumab, and combination of nivolumab with ipilimumab or nivolumab with relatlimab) are recommended for both BRAF mutation-negative and mutation-positive disease.[64,70,73,77,78] These treatment options are based on the stage of disease (unresectable or metastatic), prior treatment history, and suitability for systemic immunotherapy, with recent approvals expanding options to include first-line combinations like nivolumab-relatlimab for younger adolescent patients who are 12 and over. None of the previous technology appraisals focused on our target population of interest, i.e. post anti-PD-1 and if BRAF mutation positive, prior treatment with BRAF inhibitor +/- MEK inhibitor. Therefore, in the absence of an overlap between our target population and the populations for which current therapies are approved for, the comprehensive list of previous NICE TAs approved for the treatment of advanced melanoma were reviewed. Whilst these previous TAs do not list relevant comparators for our submission, the precedence discussed within these appraisals have been leveraged for this appraisal. The previous TAs that were reviewed are summarised in Appendix M.

1.3.8.3 Unmet clinical need

Despite the availability of treatments and their contribution to improved patient outcomes in the last decade, up to 70% of patients do not respond to these treatments or eventually relapse[79], and subsequent treatment options are limited after progression. Hence, there remains a substantial unmet need in previously treated relapsed or refractory advanced melanoma population starting from the second-line treatment setting.[58]

In patients who receive ICIs, 40-65% do not respond (primary resistance), and of those with initial disease control, more than half progress within 12 months.[2] Additionally, ICI therapy can lead to TEAEs including diarrhoea, fatigue, itching (pruritus) and nausea; approximately 36% of patients discontinue therapy due to

TEAEs.[80] Most patients (88%) develop immune-related adverse events (irAEs).[81] These differ from typical adverse reactions as they often have a delayed onset and prolonged course, involving various organ systems (including the skin system, digestive system, endocrine system, and respiratory system), with some irAEs being permanent, such as type 1 diabetes and hypophysitis.[45,46]

Furthermore, only 35-50% of patients have the relevant mutations required for the treatment with BRAF and MEK inhibitors.[2] Of these patients, approximately 15-20% fail to respond to targeted therapy, and only 22% remain progression-free at three years.[2,80] Responses are often not durable, and disease progression may be rapid on relapse.[82] Targeted therapy can lead to TEAEs including fever, diarrhoea, and colitis; the occurrence of TEAEs leads to discontinuation of treatment in 19% of cases.[83]

Both PD-1 inhibitors and BRAF/MEK inhibitors are not reimbursed in more than one LoT.[82] As such, current treatment options after progression on PD-1 inhibitors and targeted therapy remain sparse and show limited efficacy benefit to patients.

Survival outcomes for patients in the UK with advanced melanoma who have progressed after both PD-1 inhibitors and BRAF/MEK inhibitors remain extremely poor. Treatment options are highly limited and include ipilimumab monotherapy (if not previously administered alongside nivolumab in the first-line setting), chemotherapy such as dacarbazine, or BSC. A study by Mangin *et al.* (2021) assessing the clinical outcomes of cytotoxic chemotherapy in previously treated patients found that the median PFS among 50 individuals who had received prior immunotherapy was just 2.6 months and median OS of 6.9 months.[84] Furthermore, a study by Marquez-Rodas et al. (2022) assessed 186 patients (38.8%) who progressed with first line and received second line treatment, reporting a median PFS of 5.1 months and a median OS of 11.3 months.[85] Chemotherapy is not curative by its mechanism of action, and its administration raises safety and tolerability concerns, particularly in older patients.[58] Similarly, BSC, which focuses on symptom management, palliative care, palliative radiotherapy, and emotional and practical support, is not curative and has very limited/no impact on survival outcomes in advanced melanoma. Due to the short duration of PFS and low response rates,

survival outcomes with chemotherapy and BSC are not sustainable and poor, therefore these treatment options are associated with a higher economic burden with little clinical benefit to patients.

Given this, few treatment options remain following anti-PD-1 treatment, and the data to inform the decision-making, including real-world evidence, is limited. There is a clear need for more effective and tolerable options in the treatment paradigm of previously treated patients. According to UK clinical expert feedback received at an advisory board in October 2024, up to 50% of patients who are eligible for second LoT prefer to enter a clinical trial instead of receiving chemotherapy or BSC.[16] This demonstrates the substantial unmet need for therapies that are effective and safe for patients with metastatic, unresectable melanoma who have progressed on PD-1 inhibitor therapy and BRAF ± MEK inhibitor therapy (if BRAF positive).

1.4 Equality considerations

For current treatment options, there may have been an imbalance in access which raised equality concerns however, no equality considerations have been identified as yet for lifileucel.

2 Clinical effectiveness

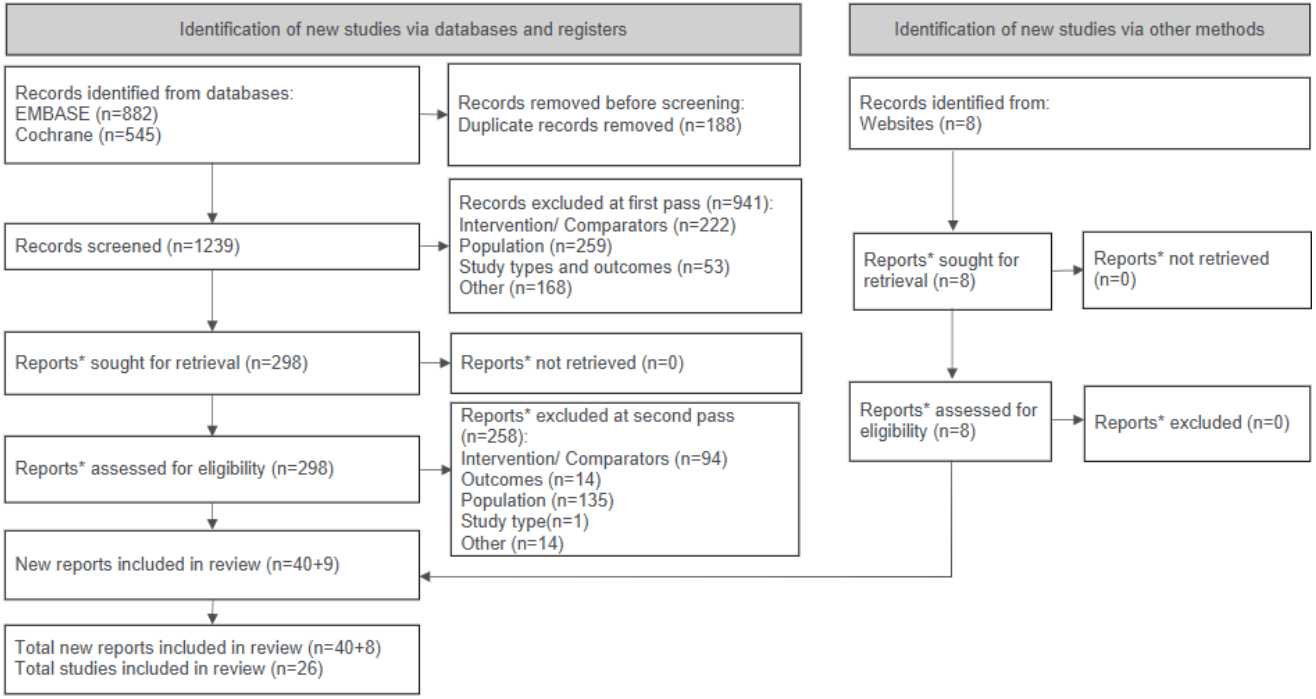
2.1 Identification and selection of relevant studies

A clinical systematic literature review (SLR) was performed in August 2024 and updated in January 2025 to identify all relevant clinical evidence to inform the indirect treatment comparison (ITC) for lifileucel versus relevant comparators (ipilimumab, chemotherapy and BSC) in patients with unresectable or metastatic melanoma. Supplementary searches of “grey” literature were performed to ensure all relevant publications of comparators of interest in the desired patient population were identified.

As presented in Figure 4, a total of 40 relevant papers were identified for ipilimumab and chemotherapy in the database searches and eight additional papers were identified in the supporting “grey” literature, resulting in 48 relevant papers reporting

26 unique studies. The methods, search strategies and eligibility criteria used, along with results and quality assessment for the SLR are provided in Appendix B.

Figure 4: Clinical SLR PRISMA flow diagram for previously treated unresectable or metastatic melanoma



Abbreviations: n, Number; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; SLR, Systematic literature review.
*Glossary of items:
• Report—A document (paper or electronic) supplying information about a particular study. It could be a journal article, preprint, conference abstract, study register entry, clinical study report, dissertation, unpublished manuscript, government report, or any other document providing relevant information
• Record—The title or abstract (or both) of a report indexed in a database or website (such as a title or abstract for an article indexed in Medline). Records that refer to the same report (such as the same journal article) are “duplicates”; however, records that refer to reports that are merely similar (such as a similar abstract submitted to two different conferences) should be considered unique.
• Study—An investigation, such as a clinical trial, that includes a defined group of participants and one or more interventions and outcomes. A “study” might have multiple reports. For example, reports could include the protocol, statistical analysis plan, baseline characteristics, results for the primary outcome, results for harms, results for secondary outcomes, and results for additional mediator and moderator analyses.
Note: the number of unique studies are listed in Appendix B, Section B.4.2.

2.2 List of relevant clinical effectiveness evidence

Due to the single-arm nature of C-144-01, the 26 unique studies identified in the SLR were assessed for inclusion in the ITC. This was based on the following criteria: studies conducted in Europe or global studies which included European sites; information on prior lines of therapy for the study population; the availability of appropriate PFS and OS KM curves.

The feasibility assessment resulted in eight studies of patients with metastatic, unresectable melanoma pretreated with anti-PD-1 therapy evaluating either lifileucel or one of the comparators of interest. One of these studies was the pivotal lifileucel study which evaluated patients with metastatic, unresectable melanoma pretreated with anti-PD-1 therapy.[86] Of the remaining studies, five studies reported on ipilimumab[87–91] and two studies on chemotherapy.[84,92] No studies relevant to BSC were identified. A summary of these studies is presented in Table 8 of Appendix B.4.5; further details on the ITC can be found in Section 2.10.

The C-144-01 trial is the primary source of data for clinical efficacy and safety of lifileucel in patients with previously treated unresectable or metastatic melanoma.[86] The data in the C-144-01 trial represent a four-year follow-up for outcomes, with a median follow-up of 27.6 months for key efficacy outcomes. A summary of this study is presented in Table 5.

Table 5: Clinical effectiveness evidence

Study	C-144-01 trial				
Study design	Phase II, open-label, multicohort, multicentre, single-arm trial				
Population	Adult patients with unresectable or metastatic melanoma treated with ≥1 systemic prior therapy including a PD-1-blocking antibody and, if BRAF V600 mutation-positive, a BRAF/MEK inhibitor				
Intervention(s)	Lifileucel: A tumour sample is resected from each patient and cultured ex vivo to expand the population of tumour-infiltrating lymphocytes. After LD, patients are infused with lifileucel followed by IL-2.				
Comparator(s)	NA				
Indicate if trial supports application for marketing authorisation	Yes	X	Indicate if trial used in the economic model	Yes	X
	No			No	

Study	C-144-01 trial
Rationale if study not used in model	NA
Reported outcomes specified in the decision problem	**PFS, OS**, response rates, **safety**, HRQoL
All other reported outcomes	NA

Note: Outcomes in **bold** are used in the economic model.
Abbreviations: HRQoL, Health-related quality of life; IL-2, Interleukin-2; LD, Lymphodepletion; MEK, Mitogen-activated protein kinase; NA, Not applicable; OS, Overall survival; PD-1, Programmed cell death 1; PFS, Progression-free survival.
Source: C-144-01 clinical pack[86]

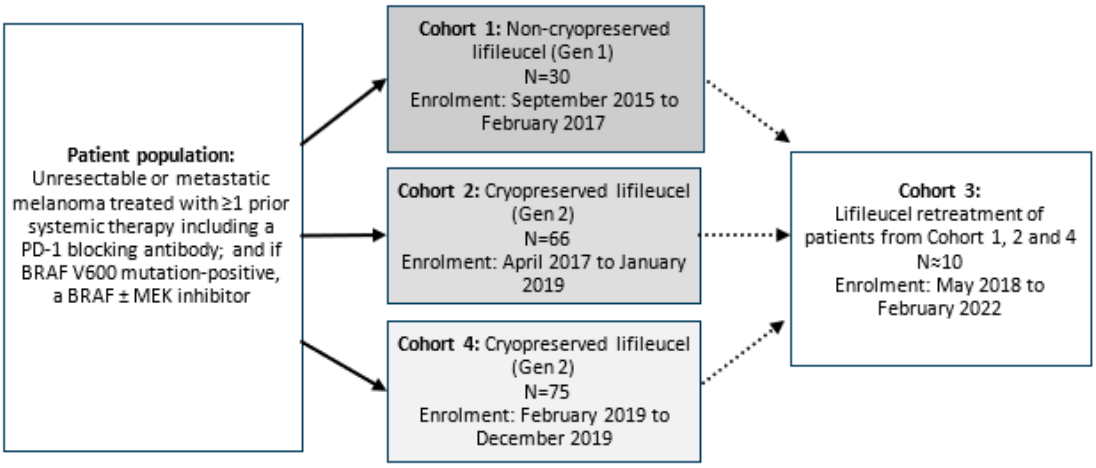
2.3 Summary of methodology of the relevant clinical effectiveness evidence

2.3.1 Study design

C-144-01 (NCT02360579) is a global Phase II, open-label, multicohort, multicentre, single-arm trial that evaluated the efficacy and safety of lifileucel in adult patients with unresectable or metastatic melanoma treated with ≥1 systemic prior therapy including a PD-1-blocking antibody and, if BRAF V600 mutation-positive, a BRAF inhibitor +/- a MEK inhibitor.[93]

The trial was composed of four distinct cohorts as shown in Figure 5[94]:

Figure 5: C-144-01 trial design



Abbreviations: Gen 1, Generation 1 T cell manufacturing process; Gen 2, Generation 2 T cell manufacturing process; PD-1, programmed cell death protein-1.
Source: Adapted from C-144-01 clinical pack[86] and Medina (2023)[95]

Given non-cryopreserved lifileucel is no longer in clinical use (Cohort 1), and the license will not include retreatment (Cohort 3), the following discussion of the C-144-01 study will focus only on patients from Cohorts 2 and 4 (N=153).[86] Cohorts 2 and 4 differ in date and period of enrolment but have the same eligibility criteria, manufacturing process and treatment. As such, the data presented in the submission represents the pooled results from Cohorts 2 and 4. Multiple analysis sets derived from the total screened patients are presented throughout the submission and are discussed in more detail in Section 2.4.1). The analysis utilised the latest data available (data cut-off [DCO]: 30th June 2023). One final efficacy data read out is expected from the trial in late-2025. Table 6 provides a summary of the C-144-01 trial methodology.

Table 6: C-144-01 trial methodology

Study	C-144-01; NCT02360579
Trial design	Global phase II, open-label, multicohort, multicentre, single-arm trial
Location	42 sites across France (2), Germany (8), Hungary (1), Spain (5), Switzerland (1), USA (21) and UK (4)
Population	Adult patients with unresectable or metastatic melanoma treated with ≥1 systemic prior therapy including a PD-1 blocking antibody; and if BRAF V600 mutation-positive, a BRAF inhibitor or BRAF inhibitor in combination MEK inhibitor
Intervention	Lifileucel (N=153): A tumour sample is resected from each patient and cultured ex vivo to expand the population of tumour-infiltrating lymphocytes. After LD, patients are infused with lifileucel followed by IL-2
Key inclusion criteria	Had diagnosis of unresectable or metastatic melanoma (Stage IIIc or Stage IV) Progressed following ≥ 1 prior 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 Had documentation of radiological disease progression after the most recent therapy Had at least 1 measurable target lesion, as defined by RECIST v1.1 Had at least 1 resectable lesion (or aggregate of lesions resected) of a minimum 1.5 cm in diameter post-resection to generate TIL; surgical removal with minimal morbidity (defined as any procedure for which expected hospitalization was ≤ 3 days) Were ≥ 18 years of age at the time of consent. Enrolment of patients > 70 years of age may have been allowed after consultation with the Medical Monitor Had an ECOG performance status of 0 or 1, and an estimated life expectancy of ≥ 3 months

	In the assessment of the investigator, were able to complete all study-required procedures Had the following hematologic parameters: Absolute neutrophil count ≥ 1000/mm^3 Hemoglobin ≥ 9.0 g/dL Platelet ≥ 100,000/mm^3 Had adequate organ function: Serum alanine transaminase /serum glutamic-pyruvic transaminase and aspartate transaminase/serum glutamic-oxaloacetic transaminase ≤ 3 times ULN; patients with liver metastasis ≤ 5 times ULN Estimated creatinine clearance ≥ 40 mL/min using the Cockcroft-Gault formula Total bilirubin ≤ 2 mg/dL Recovered from all prior therapy-related AEs to ≤ Grade 1 (per CTCAE v4.03), except for alopecia or vitiligo, prior to Enrolment (tumour resection) Had a washout period of ≥ 28 days from prior anti-cancer therapy(ies) to the start of the planned LD preconditioning regimen Patients of childbearing potential or their partners of childbearing potential must have been willing to take the appropriate precaution to avoid pregnancy or fathering a child for the duration of the study and practice an approved, highly effective method of birth control during treatment and for 12 months after receiving the last protocol-related therapy. Patients (or a legally authorised representative) must have had the ability to understand the requirements of the study, provide written informed consent as evidenced by signature on an ICF approved by IRB/IEC, and agree to abide by the study restrictions and return to the site for the required assessments, including the OS Follow-up Period
Key exclusion criteria	Were BRAF mutation-positive (V600), but had not received prior systemic therapy with a BRAF inhibitor alone or a BRAF inhibitor in combination with a MEK inhibitor Had received an organ allograft or prior cell transfer therapy (Note: patients who were screened for Cohort 3 were exempt from this criterion) Had melanoma of uveal/ocular origin Had a history of hypersensitivity to any component or excipient of lifileucel or other study drugs Had symptomatic and/or untreated brain metastases (of any size and any number) Were on chronic systemic steroid therapy for any reason Had active medical illness(es) that would pose increased risk for study participation, including: active systemic infections requiring systemic antibiotics, coagulation disorders, or other active major medical illnesses of the cardiovascular, respiratory, or immune system Had ≥ Grade 2 haemorrhage within 14 days prior to enrolment (tumour resection) Were seropositive for any of the following: HIV-1 or HIV-2 antibodies Hepatitis B antigen, hepatitis B core antibody, or hepatitis C antibody; patients with acute or chronic hepatitis infections have been enrolled if the viral load by PCR was undetectable with/without active treatment

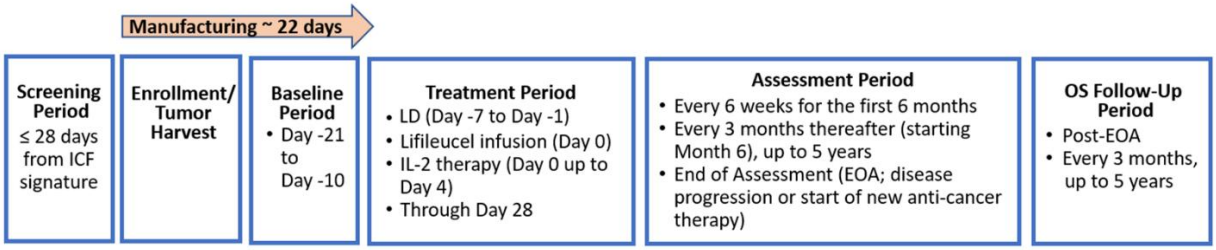
	Syphilis (rapid plasma reagin test or venereal disease research laboratory test) Cytomegalovirus IgM antibody titer or PCR assay and Epstein-Barr virus IgM or PCR assay indicating active infection Positive HSV-1 and HSV-2 IgM serology or PCR assay Had any form of primary immunodeficiency (such as severe combined immunodeficiency disease and acquired immunodeficiency syndrome) Had a left ventricular ejection fraction < 45% or New York Heart Association functional classification Class > 1 Had a documented forced expiratory volume in 1 second of ≤ 60% Had another primary malignancy within the previous 3 years (with the exception of carcinoma in situ of the breast, cervix, or bladder; localized prostate cancer; and non-melanoma skin cancer that had been adequately treated) Had received a live or attenuated vaccine within 28 days of beginning the LD preconditioning regimen Were pregnant or breastfeeding Had cancer that required immediate attention or those who would otherwise suffer a disadvantage by participating in this study Were protected by the following constraints: Hospitalized persons without consent or persons deprived of liberty because of a judiciary or administrative decision Adult persons with a legal protection measure or persons who could not express their consent Patients in emergency situations who could not consent to participate in the study
Key Endpoints	Primary: ORR (IRC), derived as the number of patients who had a BOR of CR or PR divided by the number of patients in the FAS × 100%. To determine BOR, all tumour response assessments per RECIST v1.1 up to the first PD were considered. Secondary: DOR (IRC), defined as the time (in months) from the timepoint at which the initial measurement criteria per RECIST v1.1 were met for a CR or PR, whichever response was observed first, until the first date that PD was objectively documented, or the patient expired DCR and BOR (IRC), defined as the proportion of patients who had a BOR of CR, PR, stable disease, or non-CR/non-PD, where non-CR/non-PD is only for patients without target lesions identified by the IRC PFS (IRC), defined as the time (in months) from the date of lifileucel infusion to PD or death due to any cause, whichever occurred earlier OS (IA), defined as the time (in months) from the date of lifileucel infusion to death due to any cause. ORR (IA), derived as the number of patients who had a BOR of CR or PR divided by the number of patients in the FAS × 100%. To determine BOR, all tumour response assessments per RECIST v1.1 up to the first PD were considered. TEAEs and SAEs, defined as the incidence rate of TEAEs and SAEs by severity and relationship to lifileucel. Exploratory: ORR, DOR, DCR and PFS as assessed by the Investigator per irRECIST[a]

	HRQoL, assessed using the EORTC QLQ-C30 instrument and analyses per the published evaluation manual.

[a] This endpoint was only assessed for Cohort 4 patients.
Abbreviations: AE, Adverse event; BOR, Best overall response; CR, Complete response; CTCAE, Common Terminology Criteria for Adverse Events; DCR, Disease control rate; DOR, Duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, Core 30; FAS, Full analysis set; HIV, Human immunodeficiency virus; HRQoL, health-related quality of life; HSV, Herpes simplex virus; IA, Investigator assessed; ICF, Informed consent forms; IEC, Independent Ethics Committee; IgM, Immunoglobulin M; IL-2, Interleukin-2; IRB, Institutional Review Board; IRC, Independent review committee; irRECIST, Immune-related Response Evaluation Criteria in Solid Tumours; LD, Lymphodepletion; MEK, Mitogen-activated extracellular signal-regulated kinase; ORR, Objective response rate; OS, Overall survival; PCR, Polymerase chain reaction; PD, Progressive disease; PD-1, Programmed cell death protein-1; PFS, Progression-free survival; PR, Partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SAE, Serious adverse event; TEAE, Treatment-emergent adverse event; TIL, Tumour-infiltrating lymphocytes; ULN, Upper limit of normal; USA, United States of America; UK, United Kingdom.
Source: C-144-01 clinical pack[86]

Figure 6 illustrates the course of the treatment process and post-treatment follow-up. The treatment process starts with the screening of the patient. Screened patients enter the study and have their tumours harvested. Harvesting of the tumours is followed by manufacturing, administration of the cell therapy regimen including infusion of lifileucel, then post-infusion assessment and follow-up (further described in Table 2).[86] Patients who reach the assessment period are evaluated for efficacy until either the End-of-Assessment visit (for up to five years from the lifileucel infusion), disease progression or the start of a new anti-cancer therapy. Patients who had the End-of-Assessment visit, were followed up for OS for up to five years from enrolment or until discontinuation from the study.

Figure 6: Study design chart for 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.
Abbreviations: EOA, End-of-Assessment; ICF, Informed consent form; IL-2, Interleukin-2; LD, Lymphodepletion; OS, Overall survival.
Source: Adapted from C-144-01 clinical pack[86]

2.3.2 Outcomes reported

The primary efficacy endpoint was ORR as assessed by the IRC per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1.[86] The primary endpoint and all

subsequent endpoint definitions are summarised in Table 6. Secondary efficacy endpoints included ORR as assessed by the Investigator, as well as duration of response (DOR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS). Considering the multinational and multicentre nature of this study the PFS was determined using both FDA and EMA guidelines.[96,97] In addition, safety was also assessed including TEAEs and serious adverse events (SAEs). Exploratory analyses included efficacy analyses assessed by the Investigator per immune-related RECIST (irRECIST) for Cohort 4 patients only,[86] HRQoL (measured through the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 [EORTC QLQ-C30]), time to first response and time to best response. Other analyses included COVID-19 impact and hospital resource use.

2.3.3 Baseline characteristics and disease characteristics

The demographics and baseline disease characteristics of patients in the efficacy data sets from Cohort 2, Cohort 4, and Cohorts 2 and 4 combined, in the C-144-01 trial are presented in Table 7 and Table 8, respectively,[86] (please refer to Section 2.4.1 for more details).

In the Pooled Data Aligned with Commercial Specifications (PDAwCS) efficacy set (N=106), [redacted] patient was included from a UK site.[86] The mean age was [redacted] years, with over [redacted] of patients under the age of 65. [redacted] had Stage IV melanoma at study entry and [redacted] had >3 target and non-target lesions at baseline (as assessed by IRC).

Patients received a median of [redacted] prior systemic therapies.[86] [redacted] patients had previously received anti-PD-1/PD-L1 therapy, and [redacted] had also received anti-CTLA-4 therapy. [redacted].

Table 7: Demographic characteristics for the PDAwCS efficacy set

Characteristics	Cohort 4 (N=73)	Cohort 2 (N=33)	Pooled Cohorts 2 and 4 (N=106)
Male, n (%)	38 (52.1)	[redacted]	60 (56.6)
Mean age (SD)	[redacted]	[redacted]	55.2 (11.95)
Race, n (%)			
Asian	1 (1.4)	[redacted]	[redacted]
Black or African American	2 (2.7)	[redacted]	[redacted]
White	69 (94.5)	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Mean weight (kg, SD)	[redacted]	[redacted]	[redacted]
Country, n (%)			
United States	[redacted]	[redacted]	[redacted]
France	[redacted]	[redacted]	[redacted]
Germany	[redacted]	[redacted]	[redacted]
Spain	[redacted]	[redacted]	[redacted]
United Kingdom	[redacted]	[redacted]	[redacted]

Abbreviations: BMI, Body mass index; PDAwCS, Pooled data aligned with commercial specifications; SD, Standard deviation.
Source: C-144-01 clinical pack[86]
DCO: 30Jun2023

Table 8: Baseline disease characteristics for the PDAwCS efficacy set

Characteristics	Cohort 4 (N=73)	Cohort 2 (N=33)	Pooled Cohorts 2 and 4 (N=106)
Disease metastasis at Study Entry[a], n (%)			
M0	[redacted]	[redacted]	[redacted]
M1a	[redacted]	[redacted]	[redacted]
M1b	[redacted]	[redacted]	[redacted]
M1c	[redacted]	[redacted]	[redacted]
M1d	[redacted]	[redacted]	[redacted]
Patients with baseline Liver and/or Brain Lesions by IRC, n (%)	[redacted]	[redacted]	[redacted]
Patients with Mucosal Melanoma, n (%)	[redacted]	[redacted]	[redacted]
Stage at study entry, n (%)			
IIIC	[redacted]	[redacted]	10 (9.4)
IV	[redacted]	[redacted]	96 (90.6)
Baseline ECOG Score[a], n (%)			

0	41 (56.2)	[redacted]	56 (52.8)
1	32 (43.8)	[redacted]	50 (47.2)
≥2	0	[redacted]	0
Resected tumour site, n (%)			
Lymph Node	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Skin/Subcutaneous	[redacted]	[redacted]	[redacted]
Liver	[redacted]	[redacted]	[redacted]
Lung	[redacted]	[redacted]	[redacted]
Other Visceral	[redacted]	[redacted]	[redacted]
Peritoneal/Retroperitoneal	[redacted]	[redacted]	[redacted]
Breast	[redacted]	[redacted]	[redacted]
Musculoskeletal	[redacted]	[redacted]	[redacted]
% PD-L1 TPS per central laboratory, n (%)			
PD-L1 Positive (TPS ≥1%)	[redacted]	[redacted]	[redacted]
PD-L1 Negative (TPS <1%)	[redacted]	[redacted]	[redacted]
PD-L1 Positive (TPS ≥5%)	17 (23.3)	[redacted]	[redacted]
PD-L1 Negative (TPS <5%)	[redacted]	[redacted]	[redacted]
BRAF status, n (%)			
Positive	20 (27.4)	[redacted]	[redacted]
Negative	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Baseline LDH (U/L), n (%)			
<ULN	[redacted]	[redacted]	50 (47.2)
>1 - ≤ 2 x ULN	[redacted]	[redacted]	32 (30.2)
> 2 x ULN	[redacted]	[redacted]	24 (22.6)
Prior therapy category, n (%)			
Anti-CTLA-4	63 (86.3)	[redacted]	[redacted]
Anti-PD-1/PD-L1	73 (100)	[redacted]	[redacted]
Anti-PD-1/CTLA-4 Combo	42 (57.5)	[redacted]	[redacted]
BRAF/MEK Inhibitor[b]	20 (27.4)	[redacted]	[redacted]
IL-2	[redacted]	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]
Mean number of prior therapies (SD)	3.3 (1.69)	[redacted]	[redacted]

Number of Baseline Target and Non-target Lesions Assessed by IRC, n (%)			
≤3	[redacted]	[redacted]	[redacted]
>3	[redacted]	[redacted]	[redacted]

[a] Baseline value is defined as the last assessment on or before the first dose of LD.
[b] Includes patients who have BRAF V600E or V600K mutated melanoma and received a BRAF inhibitor ± a MEK inhibitor.
Abbreviations: CTLA-4, Cytotoxic T-lymphocyte-associated antigen-4; ECOG, Eastern Cooperative Oncology Group; IL-2, Interleukin-2; IRC, Independent review committee; LD, Lymphodepletion; LDH, Lactate dehydrogenase; max, Maximum; MEK, Mitogen-activated extracellular signal-regulated kinase; min, Minimum; NA, Not available; PD, Progressive disease; PD-1, Programmed cell death protein-1; PDAwCS - Pooled data aligned with commercial specifications; PD-L1, Programmed death-ligand 1; SD, Standard deviation; TPS, Tumour proportion score; ULN, Upper limit of normal.
Source: C-144-01 clinical pack[86]
DCO: 30Jun2023

It is important to note that there are some differences between Cohort 2 and 4. Given that a higher proportion of patients in Cohort 4 are Stage IV than Stage IIIc, have elevated baseline lactate dehydrogenase (LDH) and have a higher baseline liver and/or brain lesions than patients in Cohort 2, Cohort 4 has a higher disease burden, which may result in patients being more difficult to treat than Cohort 2.[86] However, there are similar demographics across the cohorts in terms of disease characteristics, including baseline ECOG score and BRAF mutation status, and median number of prior therapies which support the appropriateness of pooling the data. Therefore, Cohort 2 and 4 data obtained from the clinical trial are presented as both separated and pooled. The overall demographics and baseline characteristics of the PDAwCS set (N=106) are aligned with the FAS (N=153) population (i.e. all patients who had received lifileucel that met the manufacturing product specifications as defined by the clinical protocol [defined further in Section 2.4.1]; baseline characteristics for the FAS can be found in Appendix K.1); where baseline demographics of the FAS (N=153) were validated by UK key opinion leaders (KOLs) as being representative of patients in UK clinical practice.[16]

2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

2.4.1 Analysis sets and participant flow

Multiple analysis sets derived from the total screened patients are presented within the submission, based on a progressively refined selection of patients based on the

lifileucel treatment received. A summary of the analysis sets is presented in Table 9, with participant flow presented in Table 10 and Figure 7.

Overall, a total of 270 patients were screened within Cohorts 2 and 4. Of these, 81 patients either failed screening or were not enrolled due to death, withdrawal or other reasons, resulting in 189 patients who had a tumour harvested (i.e. the tumour harvested [TH] set), of which 111 patients were from Cohort 4 and 78 patients were from Cohort 21. A total of 33 patients did not receive lifileucel, resulting in a Safety Analysis Set (SAS) of 156 patients, of which 89 patients were from Cohort 4 and 67 were from Cohort 2. A total of 153 patients comprises the full analysis set (FAS), which excluded patients who received product out of specification as defined by protocol; 87 patients in the FAS were from Cohort 4 and 66 were from Cohort 2.

For the 87 patients in Cohort 4 FAS, further exclusions are made to reach the efficacy set as presented in the proposed SmPC (and the FDA US Prescribing Information). A total of [redacted] were excluded for “product comparability” as they received product manufactured at a site not approved for commercial manufacturing. A further [redacted] were excluded due to infusion with a product that did not meet the recommended dosing range specified by the proposed SmPC of between 7.5 to 72 billion cells. The resultant 73 patients in Cohort 4 comprise the efficacy set for the SmPC (and the FDA US Prescribing Information) and is named the “SmPC Cohort 4 Efficacy Set”.

The same exclusions are applied to the Cohort 2 FAS to reach the “SmPC Cohort 2 Efficacy Set”. A total of [redacted] were excluded for “product comparability” as they were manufactured at a site not approved for commercial manufacturing. A further [redacted] were excluded due to receiving a product that did not meet the recommended dosing range specified by the proposed SmPC of between 7.5 to 72 billion cells. This resulted in 33 patients in the “SmPC Cohort 2 Efficacy Set”.

Together, a total of 106 patients (73 from Cohort 4 and 33 from Cohort 2) comprise the “Pooled Data Aligned with Commercial Specifications” (PDAwCS) analysis set, which forms the basis of the results in this submission and the cost-effectiveness model (CEM).

When considering only the patients with lifileucel manufactured at a commercially approved site, [redacted].

Table 9: Analysis sets derived from data in C-144-01

	Population	Outcomes from the data set used in analyses	Submission
Screened set (N=270)	All patients who had signed ICF and were screened in the study	NA	NA
TH set (Enrolled set, N=189)	All patients who had tumour resection for the production of lifileucel, regardless of whether they received lifileucel or not	Safety outcomes	Section 2.10
SAS (N=156)	All patients who received any lifileucel infusion	Safety outcomes from this analysis set are used in the model	Section 2.10 Section 3.3.3
FAS (N=153)	All patients who had received lifileucel that met the manufacturing product specifications as defined by the clinical trial protocol	PFS, OS, response rates and HRQoL	Section 2.6.3 Section 2.6.4
PDAwCS (N=106)	All patients who had received lifileucel that met proposed SmPC dosing range and manufactured at facilities approved for commercial manufacturing	PFS and OS data from this analysis set are used in the cost effectiveness model	Section 2.6.3 Section 3.3.1.5

Abbreviations: FAS, Full analysis set; HRQoL, Health-related quality of life; ICF, Informed consent form; NA, Not applicable; OS, Overall survival; PDAwCS, Pooled data aligned with commercial specifications; PFS, Progression-free survival; SAS, Safety analysis set; TH, Tumour harvested.
Source: C-144-01 clinical pack[86]

Table 10: Patient disposition in C-144-01 study for Cohorts 2 and 4

	Cohort 4 (N=111)	Cohort 2 (N=78)	Pooled Cohorts 2 and 4 (N=189)
Screened patients	161 (100)	109 (100)	270 (100)
TH Set (Enrolled Set), n (%)	111 (68.9)	78 (71.6)	189 (70)
Patients who did not receive lifileucel	22 (19.8)	11 (14.1)	33 (17.5)
SAS, n (%)	89 (80.2)	67 (85.9)	156 (82.5)
Patients who received lifileucel out-of-specifications	2 (2.2)	0	2 (1.3)

Patients who received lifileucel of <1x10^9 viable cells	0	1 (1.5)	1 (0.6)
FAS, n (%)	87 (97.8)	66 (98.5)	153 (98.1)
Patients who received lifileucel of <7.5x10^9 or >72x10^9 viable cells	[redacted]	[redacted]	[redacted]
Patients who received lifileucel from manufacturing facilities not approved for commercial manufacturing	[redacted]	[redacted]	[redacted]
PDAwCS, n (%)	73 (83.9)	33 (50)	106 (69.3)

Percentages given as a proportion of the previous analysis set,
Abbreviations: FAS, Full analysis set; PDAwCS, Pooled data aligned with commercial specifications; SAS, Safety analysis set; TH, Tumour harvested.
Source: C-144-01 clinical pack[86]
DCO: 30Jun2023

Figure 7: Schematic flow of patients C-144-01 study and steps to generate different analysis sets from Cohorts 2 and 4

Abbreviations: PDAwCS, Pooled data aligned with commercial specifications; TH, Tumour harvested.
Source: Adapted from C-144-01 clinical pack[86]
DCO: 30Jun2023

2.4.2 Statistical analysis

The statistical analyses used for the primary endpoints of the C-144-01 trial, along with the sample size calculations and the handling of missing data, are presented in Table 11. The null hypothesis was tested versus the alternative hypothesis at a significance level of 5% (2-sided).[86] The null hypothesis was rejected if the lower bound of the 2-sided 95% Clopper-Pearson confidence interval (CI) for ORR> 10%. As the null hypothesis for Cohort 4 was rejected, a secondary hypothesis testing of the primary efficacy endpoint was performed based on the Pooled Cohorts 2 and 4 as supportive evidence of effectiveness for lifileucel.

Table 11: Statistical methods for the C-144-01 trial for the FAS

Primary hypothesis for Cohort 4	Null hypothesis: ORR ≤ 10% Alternative hypothesis: ORR >10%
Secondary hypothesis for Pooled Cohorts 2 and 4[a,b]	Null hypothesis: ORR ≤10% Alternative hypothesis: ORR >10%
Statistical analysis	All binary endpoints were summarised with a point estimate and corresponding 2-sided 95% CI, calculated using the Clopper-Pearson Exact method. For time-to-event endpoints, the KM method was applied to estimate the survival function, median duration, and event-free rates at specified time points. Two-sided 95% CIs for median time-to-event were constructed using log-log transformation. Finally, baseline scores, post-baseline scores, and change from baseline for each scale and individual item measure were descriptively summarised at each timepoint.
Sample size, power and calculation	The planned sample size for Cohort 4 was 75 patients, providing >90% power to detect statistical significance at a two-sided significance level of 0.05, using the exact test. This calculation assumed a true response rate of 25% for TIL cell therapy in this population. As a sensitivity analysis, ORR assessed by the IRC was also estimated for patients in the TH set.
Data management, patient withdrawal	Missing individual data were treated as absent and no values were imputed, thus calculations were based on available data only. When handling incomplete data, usually involving safety data, a conservative approach was applied for the calculation. Any missing data related to the COVID-19 pandemic were documented and analysed as part of the investigation of COVID-19's impact on the study.

a This hypothesis was considered if the null hypothesis for Cohort 4 was rejected.
b Cohort 2 was not assessed as it was not registered for the FDA.
Abbreviations: CI, Confidence interval; FAS, Full analysis set; IRC, Independent review committee; KM, Kaplan-Meir; ORR, Objective response rate; TH, Tumour harvested; TIL, Tumour-infiltrating lymphocytes.
Source: C-144-01 clinical pack[86]

2.5 Critical appraisal of the relevant clinical effectiveness evidence

Quality assessment of the C-144-01 trial has been conducted using the Downs and Black Checklist for Clinical Trial Quality Assessment for non-RCTs and is provided in Appendix K.2.[2,98] This checklist is in-line with NICE guidelines.[99] Based on the findings from the quality assessment, the C-144-01 trial was a well-designed single arm trial with the appropriate steps taken to minimise bias where possible.

2.6 Clinical effectiveness results of the relevant studies

2.6.1 Overview of key efficacy outcomes

Key efficacy outcomes of patients with metastatic melanoma in the C-144-01 trial over the 4-year follow-up are presented in Table 12 and Table 13 for the PDAwCS efficacy set and FAS, respectively. The median follow-up for the PDAwCS efficacy set was 44.0 months, 55.7 months and 47.4 months for Cohort 4, Cohort 2, and Pooled Cohort 2 and 4, respectively.[86]

Table 12: Key efficacy outcomes reported in C-144-01 for the PDAwCS efficacy set

	Cohort 4 only (N=73)	Cohort 2 only (N=33)	Pooled Cohort 2 and 4 (N=106)
ORR assessed by IRC (%) (95% CI)	[redacted]	[redacted]	[redacted]
PFS			
Progressive disease and death, n (%)	[redacted]	[redacted]	[redacted]
PFS assessed by IRC, median months (95% CI)	[redacted]	[redacted]	[redacted]
OS			
Deaths (%)	[redacted]	[redacted]	[redacted]
OS assessed by investigator, median months (95% CI)	[redacted]	[redacted]	[redacted]
DCR			
DCR assessed by IRC, % (95% CI)	[redacted]	[redacted]	[redacted]

Abbreviations: CI, Confidence interval; DCR, Disease control rate; INV, Investigator; IRC, Independent review committee; ORR, Objective response rate; OS, Overall survival; PDAwCS, Pooled data aligned with commercial specifications; PFS, Progression-free survival.
Source: C-144-01 clinical pack[86]
DCO: 30June2023

Table 13: Key efficacy outcomes reported in C-144-01 for the FAS

	Cohort 4 only (N=87)	Cohort 2 only (N=66)	Pooled Cohort 2 and 4 (N=153)
ORR			
ORR assessed by IRC, % (95% CI)	28.7 (19.5,39.4)	34.8 (23.5, 47.6)	31.4 (24.1, 39.4)
ORR assessed by INV, % (95% CI)	[redacted]	[redacted]	[redacted]
PFS			
Progressive disease and death, n (%)	[redacted]	[redacted]	[redacted]
PFS assessed by IRC, median months (95% CI)	[redacted]	[redacted]	[redacted]
OS			
Deaths, n (%)	[redacted]	[redacted]	115 (75.2)
OS assessed by investigator, median months (95% CI)	[redacted]	[redacted]	13.9 (10.6, 17.8)
DOR			
DOR assessed by IRC, median months (95% CI)	[redacted]	[redacted]	[redacted]
DCR			
DCR assessed by IRC, % (95% CI)	[redacted]	[redacted]	[redacted]

Abbreviations: CI, Confidence interval; DCR, Disease control rate; DOR, Duration of response; FAS, Full analysis set; INV, Investigator; IRC, Independent review committee; ORR, Objective response rate; OS, Overall survival; PFS, Progression-free survival.
Source: Medina et al. (2023)[95]; C-144-01 clinical pack[86]
DCO: 30June2023

2.6.2 Primary endpoint: objective response rate by the independent review committee

As presented in Table 14, lifileucel met its primary efficacy endpoint for the PDAwCS efficacy set with an ORR as assessed by the IRC of [redacted] in Pooled Cohorts 2 and 4.[86]

This highlights the potential of lifileucel as an effective intervention, significantly enhancing response rates in patients with Stage IIIC-IV melanoma who are heavily pretreated, with limited remaining treatment options. By surpassing the pre-specified efficacy threshold, lifileucel demonstrates promising clinical utility in delivering meaningful responses that extend survival and provide symptom relief; this can be assumed to ultimately support improved QoL for patients facing this disease. This is further corroborated by best overall response (BOR), with the [redacted] of patients

achieving stable disease (SD; [redacted] partial response (PR; [redacted] and complete response (CR; [redacted][86]

Similar results were observed in the FAS, with an IRC-assessed ORR of 31.4% [redacted] and 46.4% of patients achieving SD, 25.5% achieving PR and 5.9% achieving CR (presented in Table 15).[94] The summary of ORR as assessed by IRC are presented in Table 14 and Table 15 for the PDAwCS efficacy set and FAS, respectively.

Table 14: ORR as assessed by the IRC for the PDAwCS efficacy set

	Cohort 4 only (N=73)	Cohort 2 only (N=33)	Pooled Cohort 2 and 4 (N=106)
ORR			
ORR, n (%) (95% CI)	[redacted]	[redacted]	[redacted]
BOR, n (%)			
CR	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
NN	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]
NE	[redacted]	[redacted]	[redacted]

Abbreviations: BOR, Best of response; CI, Confidence interval; CR, Complete response; IRC, Independent review committee; NE, Not evaluable; NN, Non-CR/Non-PD; ORR, Objective response rate; PD, Progressive disease; PDAwCS, Pooled data aligned with commercial specifications; PR, Partial response; SD, Stable disease.
Source: C-144-01 clinical pack[86]
DCO: 30June2023

Table 15: ORR as assessed by the IRC for the FAS

	Cohort 4 (N=87)	Cohort 2 (N=66)	Pooled Cohorts 2 and 4 (N=153)
ORR			
ORR, n (%) (95% CI)	25 (28.7) (19.5, 39.4)	23 (34.8) (23.5, 47.6)	48 (31.4) (24.1, 39.4)
BOR, n (%)			
CR	[redacted]	5 (7.6)	9 (5.9)
PR	[redacted]	18 (27.3)	39 (25.5)
SD	[redacted]	24 (36.4)	71 (46.4)
NN	[redacted]	1 (1.5)	[redacted]

PD	[redacted]	15 (22.7)	27 (17.6)
NE	[redacted]	3 (4.5)	[redacted]

Abbreviations: BOR, Best of response; CI, Confidence interval; CR, Complete response; FAS, Full analysis set; IRC, Independent review committee; NE, Not evaluable; NN, Non-CR/Non-PD; ORR, Objective response rate; PD, Progressive disease; PR, Partial response; SD, Stable disease.
Source: C-144-01 clinical pack[86]
DCO: 30June2023

2.6.3 Secondary endpoints

2.6.3.1 Objective response rate by the Investigator

The ORR assessed by the Investigator for FAS Pooled Cohorts 2 and 4 demonstrated an [redacted] when compared to the primary outcome, further demonstrating the clinical effectiveness of lifileucel in improving response rate for patients with Stage IIIc-IV melanoma.[86] When assessed by Investigator, the concordance rate was [redacted]

The summary of ORR as assessed by Investigator for each of Cohorts 2 and 4, and in pooled Cohorts 2 and 4 is presented in Table 16 for FAS. Given the concordance between the PDAwCS efficacy set and when assessed by IRC, it is assumed results between the efficacy sets will be similar when assessed by Investigator.

Table 16: ORR as assessed by INV for the FAS

	Cohort 4 (N=87)	**Cohort 2 (N=66)**	**Pooled Cohorts 2 and 4 (N=153)**
ORR			
ORR, n (%) (95% CI)	[redacted]	[redacted]	[redacted]
BOR n (%)			
CR	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]
NE	[redacted]	[redacted]	[redacted]

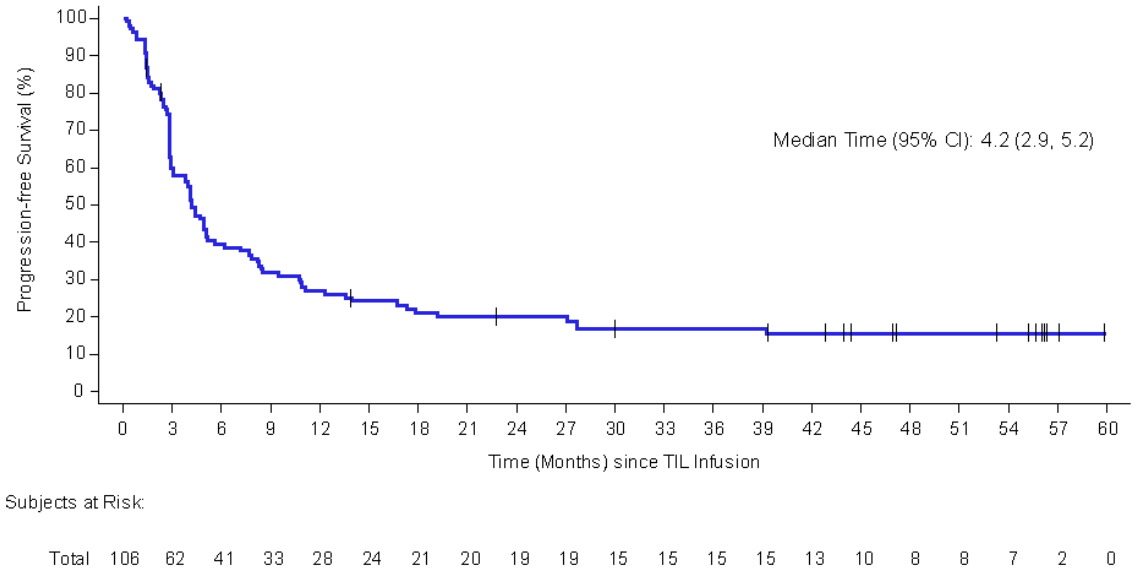
Abbreviations: BOR, Best of response; CI, Confidence interval; CR, Complete response; FAS, Full analysis set; INV, Investigator; NE, Not evaluable; NN, Non-CR/Non-PD; ORR, Objective response rate; PD, Progressive disease; PR, Partial response; SD, Stable disease.
Source: C-144-01 clinical pack[86]
DCO: 30June2023

2.6.3.2 Progression-free survival

The PDAwCS efficacy set had a median follow-up of 47.4 months. The median PFS as assessed by the IRC was [redacted] in the Pooled Cohorts 2 and 4, with a 1-year PFS rate of [redacted] and a 4-year PFS rate of [redacted] (Table 17, Figure 8).[86] This confirms the durability of efficacy demonstrated by lifileucel.

Similarly, the FAS had a median follow-up of [redacted] with a median PFS of [redacted] according to assessment by the IRC [redacted] a 1-year PFS rate of [redacted] and a 4-year rate of [redacted] as presented in Appendix K.3.[86]

Figure 8: KM curve of PFS as assessed by the IRC for the PDAwCS efficacy set



Vertical lines denote censoring.
Abbreviations: CI, Confidence interval; IRC, Independent review committee; KM, Kaplan-Meier; PDAwCS, Pooled data aligned with commercial specifications; PFS, Progression-free survival; TIL, Tumour infiltrating lymphocytes.
Source: C-144-01 clinical pack[86]
DCO: 30Jun2023

Table 17: PFS as assessed by the IRC for the PDAwCS efficacy set

	Cohort 4 (N=73)	Cohort 2 (N=33)	Pooled Cohorts 2 and 4 (N=106)
Events, n (%)	[redacted]	[redacted]	[redacted]
Progressive disease, n (%)	[redacted]	[redacted]	[redacted]
Death, n (%)	[redacted]	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]	[redacted]

Time to event[a], months			
Median (95% CI)	[redacted]	[redacted]	[redacted]
PFS Rate (%) (95% CI)[a]			
PFS at 3 months	[redacted]	[redacted]	[redacted]
PFS at 6 months	[redacted]	[redacted]	[redacted]
PFS at 9 months	[redacted]	[redacted]	[redacted]
PFS at 12 months	[redacted]	[redacted]	[redacted]
PFS at 18 months	[redacted]	[redacted]	[redacted]
PFS at 24 months	[redacted]	[redacted]	[redacted]
PFS at 30 months	[redacted]	[redacted]	[redacted]
PFS at 36 months	[redacted]	[redacted]	[redacted]
PFS at 42 months	[redacted]	[redacted]	[redacted]
PFS at 48 months	[redacted]	[redacted]	[redacted]

[a]Based on KM curve estimates.
Abbreviations: CI, Confidence interval; IRC, Independent review committee; KM, Kaplan-Meir; NR, Not reported; PD, Progressive disease; PDAwCS, Pooled data aligned with commercial specifications; PFS, Progression-free survival.
Source: C-144-01 clinical pack[86]
DCO: 30June2023

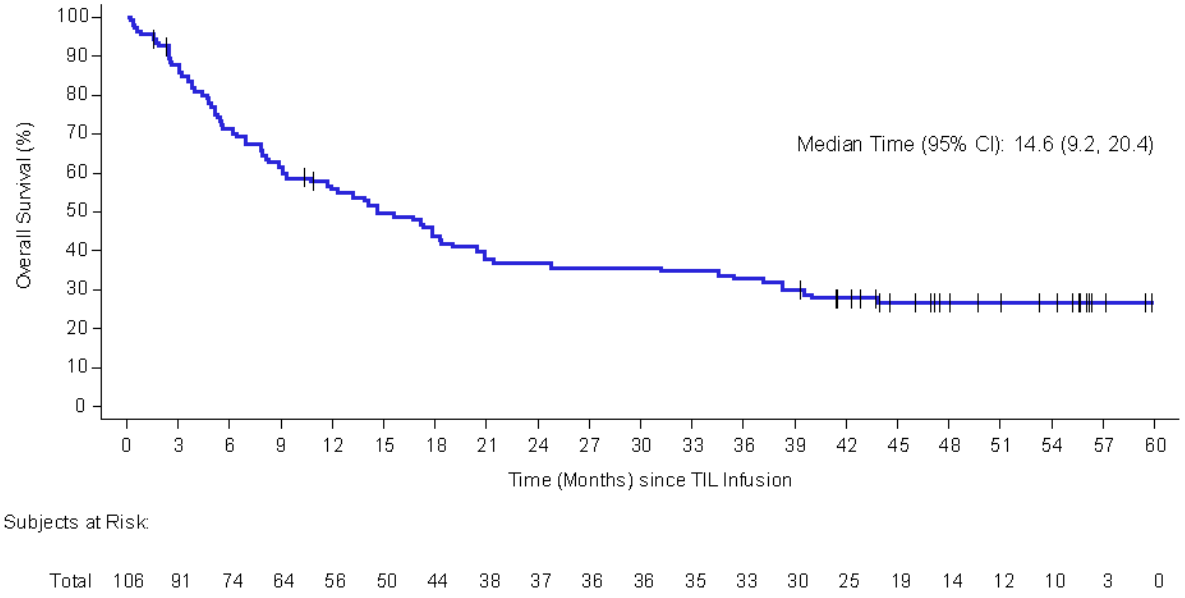
2.6.3.3 Overall survival

The PDAwCS efficacy set had a median follow-up of 47.4 months in the Pooled Cohorts 2 and 4.[86] The median OS was [redacted] with 12-month OS rate of [redacted] as presented in Figure 9 and Table 18.

Of note, [redacted] from the PDAwCS efficacy set survived at least four years, highlighting the potential to provide a durable response and extend survival significantly for these long-term survivors with Stage IIIc-IV melanoma.[86]

The FAS had a median follow-up of 48.1 months in the Pooled Cohorts 2 and 4. Similarly, the median OS was 13.9 months (95% CI: 10.6, 17.8), with 12-month OS rate of 54.0% (95% CI: 45.6%, 61.6%) as presented in Appendix K.3 for the FAS.[95]

Figure 9: KM curve of OS as assessed by investigator for the PDAwCS efficacy set



Vertial lines denote censoring.
Abbreviations: CI, Confidence interval; KM, Kaplan-Meier; OS, Overall survival; PDAwCS, Pooled data aligned with commercial specifications; TIL, Tumour infiltrating lymphocytes.
Source: C-144-01 clinical pack[86]
DCO: 30Jun2023

Table 18: OS as assessed by investigator for the PDAwCS efficacy set

	Cohort 4 (N=73)	Cohort 2 (N=33)	Pooled Cohorts 2 and 4 (N=106)
Death, n (%)	[redacted]	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]	[redacted]
Time to Death[a], months			
Median (95% CI)	[redacted]	[redacted]	[redacted]
OS Rate (%) (95% CI)[a]			
OS at 3 months	[redacted]	[redacted]	[redacted]
OS at 6 months	[redacted]	[redacted]	[redacted]
OS at 9 months	[redacted]	[redacted]	[redacted]
OS at 12 months	[redacted]	[redacted]	[redacted]
OS at 18 months	[redacted]	[redacted]	[redacted]
OS at 24 months	[redacted]	[redacted]	[redacted]
OS at 30 months	[redacted]	[redacted]	[redacted]
OS at 36 months	[redacted]	[redacted]	[redacted]
OS at 42 months	[redacted]	[redacted]	[redacted]
OS at 48 months	[redacted]	[redacted]	[redacted]
Study Follow-up Time[b], months			

Median (95% CI)	[redacted]	[redacted]	47.4 (44.5, 54.3)

[a]Based on KM curve estimates.
[b]Based on the reverse KM method.
Abbreviations: CI, Confidence interval; KM, Kaplan-Meir; OS, Overall survival; PDAwCS, Pooled data aligned with commercial specifications.
Source: C-144-01 clinical pack[86]
DCO: 30Jun2023

2.6.3.4 Duration of response

The median DOR of lifileucel in the Pooled Cohorts 2 and 4 for FAS was [redacted]. The median follow-up was [redacted]s. The probability of remaining in response at 12 months was [redacted]%, at 24 months was [redacted]%, at 36 months was [redacted]%, and at 48 months was [redacted]%.86 Additionally, the KM curve displayed in Figure 10 shows a deep and durable response, where patients who respond in the first year are likely to continue to respond long-term.

The summary of DOR as assessed by IRC for Cohorts 2 and 4, separately and the Pooled Cohorts 2 and 4 in FAS are presented in Table 19. The DOR results were similar when assessed by Investigator for all cohorts and are presented in Appendix K.3.

Figure 10: KM curve for DOR as assessed by the IRC for the FAS

[redacted]

Vertical lines denote censoring.
Abbreviations: CI, Confidence interval; DOR, Duration of response; FAS, Full analysis set; IRC, Independent review committee; KM, Kaplan-Meier; NR, Not reached.
Source: C-144-01 clinical pack[86]
DCO: 30Jun2023

Table 19: Duration of response as assessed by IRC for the FAS

	Cohort 4 (N=25)	**Cohort 2 (N=23)**	**Pooled Cohorts 2 and 4 (N=48)**
Events, n (%)	[redacted]	[redacted]	[redacted]
Progressive disease, n (%)	[redacted]	[redacted]	[redacted]
Death, n (%)	[redacted]	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]	[redacted]
DOR[a], months			
Median (95% CI)	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]

DOR[b], n (%)			
DOR ≥ 6 months	[redacted]	[redacted]	[redacted]
DOR ≥ 9 months	[redacted]	[redacted]	[redacted]
DOR ≥ 12 months	[redacted]	[redacted]	[redacted]
DOR ≥ 15 months	[redacted]	[redacted]	[redacted]
DOR ≥ 18 months	[redacted]	[redacted]	[redacted]
DOR ≥ 24 months	[redacted]	[redacted]	[redacted]
DOR ≥ 30 months	[redacted]	[redacted]	[redacted]
DOR ≥ 36 months	[redacted]	[redacted]	[redacted]
DOR ≥ 42 months	[redacted]	[redacted]	[redacted]
DOR ≥ 48 months	[redacted]	[redacted]	[redacted]
Follow-up time for Response[c], months			
Median (95% CI)	[redacted]	[redacted]	[redacted]

[a]Based on KM curve estimates
[b]Based on the observed rate
[C]Based on the reverse KM method
Abbreviations: CI, Confidence interval; DOR, Duration of response; FAS, Full analysis set; IRC, Independent review committee; KM, Kaplan-Meir; max, Maximum; min, Minimum; NR, Not reached; PD, Progressive disease.
Source: C-144-01 clinical pack[86]
DCO: 30Jun2023

2.6.3.5 Disease control rate

In the PDAwCS efficacy set for Pooled Cohorts 2 and 4, lifileucel demonstrated a DCR of [redacted] indicating prolonged periods of disease stability or regression. In the FAS for Pooled Cohorts 2 and 4, lifileucel demonstrated a DCR of [redacted].[86] In the FAS for Pooled Cohorts 2 and 4, [redacted] of patients (N=[redacted]) experienced tumour size reductions based on the change in target lesion sum of diameter from baseline as assessed by the IRC. Of note, [redacted] of those patients experienced a substantial reduction of more than 30% tumour size (Figure 11). This is expected to result in tangible clinical benefits, such as symptom relief, improved QoL (further detailed in Section 2.6.4), and the potential to delay or avoid further disease progression.

The DCR as assessed by the IRC for all cohorts of interest are summarised in Table 20 for the PDAwCS efficacy set and Figure 11 for the FAS. The DCR and tumour size assessment results were similar when assessed by Investigator for FAS in all cohorts and are presented in Appendix K.3.

Table 20: DCR as assessed by the IRC

	Cohort 4	Cohort 2	Pooled Cohorts 2 and 4
PDAwCS efficacy set			
Patients included, N	73	33	106
DCR, n (%) (95% CI)	[redacted]	[redacted]	[redacted]
FAS			
Patients included, N	[redacted]	[redacted]	[redacted]
DCR, n (%) (95% CI)	[redacted]	[redacted]	[redacted]

Note: 95% CI is calculated using the Clopper-Pearson Exact test.
Abbreviations: CI, Confidence interval; CR, Complete response; DCR, Disease control rate; FAS – Full analysis set; IRC, Independent review committee; PDAwCS, Pooled data aligned with commercial specifications.
Source: C-144-01 clinical pack[86]
DCO: 30Jun2023

Figure 11: Best percentage change from baseline for target lesion sum of diamater as assessed by the IRC for the FAS

[redacted]

Note: Patients in the FAS but not included in the figure: 6 NE patients who had no post-TIL target lesion SoD measurements (5 patients due to early death; 1 patient due to new anti-cancer therapy); 1 non CR/non PD patient (no acceptable target lesions by IRC); 6 PD patients (3 patients had no acceptable target lesions by IRC; 3 patients had no post-TIL target lesion SoD measurements on or before their PD date).
Abbreviations: CR, Complete response; FAS, Full analysis set; IRC, Independent review committee; PD, Progressive disease; PR, Partial response; SD, Stable disease; SoD, Sum of diameter; TIL, Tumour-infiltrating lymphocytes.
Source: C-144-01 clinical pack[86]
DCO: 30Jun2023

2.6.4 Exploratory endpoints

2.6.4.1 Health-related quality of life

Among patients with both baseline and Week 12 data, the mean (SD) global health status/HRQoL scores were similar throughout all cohort analyses, with baseline and Week 12 values of 69.2 (20.5) and 70.1 (21.2) respectively for pooled Cohorts 2 and 4; results in the individual cohorts were similar (presented in Appendix K.3).[86] While a decrease in QoL may occur directly after or during treatment with lifileucel, the consistent global health scores presented by the patients across the first three-month treatment period suggests that such a decrease would quickly subside and, as such, lifileucel effectively maintains patients' QoL both during and after treatment.

This additionally indicates that patients are able to preserve their overall well-being, emotional and physical functioning while performing daily activities relatively quickly following therapy. For patients, this is a meaningful benefit, as it implies that patients can manage their overall condition with minimal disruption to their routines and everyday life.

Among patients with both baseline and Month 6 data, the mean (SD) global health status/HRQoL scores were 73.4 (20.5) and 78.10 (18.3) respectively, for pooled Cohorts 2 and 4; results in the individual cohorts were similar. Compared with the results obtained from patients who had data at baseline and Month 3, this indicates that longer survival and potential response to treatment were associated with higher mean global health status/HRQoL scores. Furthermore, global health scores stabilize from Month 6 but show a decline starting from Month 24, which may be associated with higher fraction of deaths and progression. The impact of time to death and impact of progression on QoL data have not been analyzed due to lack of longitudinal data.

Although a more robust conclusion would be based on an RCT, which the key lifileucel trial is not, or an indirect comparison of trial results to literature, this wasn't possible due to the literature being based on patients who didn't receive immunotherapy in prior treatment lines. Empirical analyses of this data, despite the limitations, shows potential for anticipated improvements in QoL in these patients.

2.7 Subsequent treatments used in the relevant studies

A summary of subsequent treatments from the C-144-01 study is presented in Appendix K.3. In practice, there is a lack of standard of care for patients who progress after treatment with a PD-1 and a BRAF inhibitor (if appropriate); these patients are expected to be too sick to receive any active treatment and, even if they do receive treatment, are not expected to survive long. Indeed, after second-line systemic therapy, 12-month survival is just 27.1% with a median OS of just 6.8 months and median PFS of just 2.8 months at third-line.[100]

2.8 Subgroup analysis of primary endpoint in C-144-01 trial

A summary of subgroup analyses are presented in Appendix C. Overall, the primary efficacy endpoint was consistent across all pre-specified patient subgroups, confirming that treatment effect was generally uniform across different patient characteristics and conditions.[86]

2.9 Meta-analysis

A formal meta-analysis was not conducted due to the single-arm nature of the C-144-01 study. Treatment comparisons for lifileucel versus ipilimumab and lifileucel versus chemotherapy are presented in Section 2.10.

2.10 Indirect and mixed treatment comparisons

2.10.1 Analysis scope

In the absence of head-to-head clinical trial data for lifileucel versus prevalent comparators (ipilimumab, chemotherapy and BSC), an SLR was conducted in August 2024 and updated in January 2025 to identify all relevant clinical evidence to inform a possible ITC for lifileucel versus relevant comparators in patients with pretreated, unresectable or metastatic melanoma. The review was supplemented with “grey” literature searches to fill any gaps. Searches were limited from 2014 onwards to capture publications post the introduction of PD-1s in melanoma, ensuring only publications concerning the relevant treatment landscape and patient population were considered. Full details on the methods and results of the SLR are provided in Appendix B.

As described in Section 2.1, 40 relevant studies were identified for ipilimumab and chemotherapy in the clinical SLR and nine additional studies were identified in the supporting “grey” literature. No appropriate data sources reporting up-to-date efficacy data were identified for BSC within the published literature. The studies identified through the SLR were initially assessed for inclusion in a potential ITC based on the following three key criteria:

1. Studies conducted at European sites. It is considered that a UK data source would be most appropriate for informing comparator data in supporting UK health technology assessments (HTAs). However, in the absence of relevant UK data, European studies or global studies which included European sites in study enrolment were considered relevant, as management of melanoma patients across Europe is expected to be closely aligned with the UK.

2. Studies conducted on patients who received ≥1 prior systemic treatment including a PD-1 blocking antibody; and if BRAF V600 mutation-positive, who have had prior treatment with a BRAF +/- MEK inhibitor. These criteria ensured that comparators were studied in a comparable patient population to the C-144-01) trial population. Patients had to have received at least 1 prior systematic treatment, however, prior treatment distribution (i.e. number of lines or types of anti-PD-1 treatments received) was not a strict inclusion criterion due to limited data availability for comparator studies.

3. Availability of KM curves for OS and/or PFS from the comparator studies – this is a requirement for informing the outcome data used in the ITC. Without published KM curves, it would not be possible to reconstruct the time-to-event data required for the analysis.

Of the 49 studies identified, a total of seven studies covering two comparators met the initial selection criteria for the inclusion in the ITC feasibility assessment (the initial assessment is reported in Appendix B.4.5). The full assessment of these seven studies related to ipilimumab (N=5) and chemotherapy (N=2), is summarised in Table 21. Only one ipilimumab study (da Silva *et al.* [2021][88]) and one chemotherapy study (Mangin *et al.* [2021][84]) were considered most relevant for the inclusion in the ITC versus lifileucel. The remaining identified studies (N=5) were associated with a number of key issues preventing their inclusion in an ITC, as discussed below:

- Cybulska-Stopa *et al.* (2020)[90], a retrospective real-world study, included patients who only received one line of prior treatment, meaning that its subject population was treated less heavily prior to chemotherapy versus the lifileucel patient population (median number of prior LoT for combined cohorts 2 and 4

was 3.0). This is a key limitation and indication of poor overlap in patient populations for adjustment in an ITC analysis. Moreover, Cybulska-Stopa *et al.* (2020) excluded BRAF V600 mutation-positive patients who had received upfront treatment with BRAF or MEK inhibitors, and eight patients (6.9%) received BRAF/MEK inhibitors following the second-line treatment with ipilimumab.[90] While it is unclear how prior treatment with BRAF or MEK inhibitors would affect ipilimumab treatment outcomes, the population of interest for this submission must have had a prior therapy with a BRAF +/- MEK inhibitor if patients display BRAF V600 mutation. Furthermore, ECOG score was not reported in Cybulska-Stopa *et al.* (2020).[90] Given that ECOG score was listed as a key prognostic factor requiring adjustment in the ITC by clinical experts at a UK clinical advisory board conducted in October 2024 by the Company, this provides a significant limitation for utilisation of this data. Furthermore, the inability to match ECOG status prevents addressing a potential imbalance related to this prognostic factor. As a result, it was deemed that there is insufficient evidence in this study to inform an ITC versus lifileucel.

- Long *et al.* (2022)[91] is a post-hoc analysis of the KEYNOTE-006 study, which is Phase 3, open-label, multicentre RCT investigating pembrolizumab versus ipilimumab in patients with ipilimumab naïve, unresectable stage III/IV melanoma. BRAF V600 mutation positive patients who had not received prior BRAF or MEK inhibitors were allowed to be included in the study. This study is a post-hoc analysis in patients following treatment on pembrolizumab and therefore, reported only a few baseline characteristics for patients initiating ipilimumab. In addition, the PFS outcomes were not reported. Given the lack of this key information, it was deemed that there is insufficient evidence in this study to inform an ITC versus lifileucel.

- Rohaan *et al*. (2022)[89] is a Phase 3, open-label, multicentre RCT that included patients who were treatment-naive and patients who had at most one line of prior treatment, whereas in the C-144-01 trial, the population was more heavily pre-treated with a median of three prior lines of treatment (range: 1-9).

The differences in this inclusion criteria resulted in substantial differences in the baseline characteristics of patients in the studies. In Rohaan et al. (2022), patients were mostly fitter, with a higher proportion of patients (83%) with an ECOG PS of 0 compared with 54.9% of patients with ECOG PS of 1 in C-144-01.[89] A higher proportion of patients in Rohaan *et al.* (2022) had LDH levels within a normal range (83%) compared with patients in C-144-01 (45.8%).[89] LDH is an important prognostic factor as patients that have LDH levels within a normal range display better PFS and OS outcomes. The UK clinical experts during a clinical advisory board conducted by the Company in October 2024 commented that Rohaan *et al.* (2022) dataset was not suitable for an ITC due to the differences in patient baseline characteristics, and recommended the use of other studies for more robust evidence. Given that there is a misalignment in the inclusion criteria, which cannot be adjusted for, and a poor overlap in pivotal prognostic factors between studies, the use of Rohaan *et al.* (2022) in an ITC versus lifileucel was not considered feasible.

- Wilson *et al.* (2021)[87] is a UK-based retrospective real-world study in patients treated with sequential immunotherapy versus patients who received dual immunotherapy. This study had a small population size (N=11) for the ipilimumab-monotherapy arm. There was no data reported for key prognostic factors or treatment effect modifiers in this study. Hence, the lack of baseline characteristic data and small patient population made this study unsuitable for use in an ITC.

- Marquez-Rodas *et al*. (2022)[85], a prospective observational real-world study, reported limited inclusion criteria and baseline patient characteristics. Data on previous anti-PD-1 treatment used was not reported, and patients included in the study received at most one line of prior treatment, whereas in the C-144-01 trial, the population was more heavily pre-treated. Moreover, the study only included 29 BRAF wild-type patients and four BRAF-mutated patients who received chemotherapy (dacarbazine [N=15], platinum-based [N=11], fotemustine [N=3], or other [N=4]) following a prior anti-PD-1-based treatment. The PFS and OS KM curves were not presented for the whole study

population, but they were reported on a subgroup basis according to patients' mutation status (BRAF wild-type versus BRAF mutated). Given the limited available data and small patient population, the use of Marquez-Rodas *et al*. (2022) to inform an ITC versus lifileucel was not considered feasible.

As such, da Silva *et al*. (2021)[88] and Mangin *et al.* (2021)[84] were the only sources identified in the SLR that were deemed suitable for inclusion in the ITC for comparator treatments (ipilimumab and chemotherapy, respectively) versus lifileucel.

Source used to inform the ipilimumab effectiveness data

In da Silva *et al.* (2021)[88], the baseline characteristics of patients were well reported for all but one of the key prognostic factors and treatment-effect modifiers (target lesion sum of diameter) and mostly aligned with the inclusion/exclusion criteria for the C-144-01 population. The methods to measure PFS and OS and reported outcomes were consistent with C-144-01, however it is unclear whether PFS was assessed by IRC. Clinical experts in attendance at a UK clinical advisory board conducted in October 2024 by the Company commented on da Silva *et al.* (2021) as an appropriate source of data for patient characteristics and outcomes of patients receiving ipilimumab for pretreated advanced melanoma in the UK.[16] Given the alignment in the study design with C-144-01, as well as the similarity in baseline characteristics, da Silva *et al.* (2021) was considered the most appropriate data source for ipilimumab to inform the ITC versus lifileucel.

Source used to inform the chemotherapy effectiveness data

Given the lack of other available studies investigating the use of chemotherapy in the population of interest, Mangin *et al.* (2021)[84] was considered as the only relevant source to inform the chemotherapy population based on the following strengths:

- The chemotherapy regimens used included dacarbazine and temozolomide, which reflect the comparator treatments listed in the final NICE scope.
- The inclusion criteria for the patient population in the study was similar to criteria used for the C-144-01 population.

Hence, Mangin *et al.* (2021)[84] was considered to be a relevant source to inform the ITC. However, the study had a small sample size, with only 50 patients included who received chemotherapy (dacarbazine [N=28), temozolomide [N=21], or fotemustine [N=1]) following prior treatment with an ICI. Population-adjusted ITC analyses often require a larger sample size in order to minimize the uncertainty on the treatment effect. Using a sample as small as 50 patients means that the comparison places reliance on a small number of data, resulting in uncertainty in the analysis outputs. Therefore, given this limitation, it was not feasible to use Mangin *et al.* (2021) in a population-adjusted indirect comparison versus lifileucel. Instead, a naïve, unadjusted indirect comparison was conducted versus chemotherapy. Despite the inherent limitations of an unadjusted analysis, the results were presented for transparency to reflect the most relevant comparison available for lifileucel versus chemotherapy.

Table 21: Assessment of studies identified in the SLR for use in the ITC

Publication source (author, year)	Trial name/ NCT number	Study type	Population	Rationale for exclusion from ITC
Ipilimumab (N=5)				
Cybulska-Stopa *et al.* (2020)[90]	NR	RWE	Patients with unresectable or metastatic melanoma who had received first-line treatment with nivolumab or pembrolizumab, and second-line treatment with ipilimumab	Patients only received one prior LoT Inclusion of BRAF V600 mutation positive patients who had not received BRAFi/MEKi
da Silva *et al.* (2021)[88]	NR	Retrospective cohort study	Patients with unresectable metastatic melanoma who had received previous anti-PD-(L)1 monotherapy (nivolumab, pembrolizumab, or atezolizumab)	N/A
Long *et al.* (2022)[91]	KEYNOTE-006 (NCT01866319)	RCT	Patients with unresectable or metastatic melanoma who had completed or discontinued pembrolizumab after one or more dose and received ipilimumab or BRAFi/MEKi as first subsequent systemic therapy	BRAF V600 mutation positive patients who had not received BRAFi/MEKi were included Only a few baseline characteristics were reported for the population of interest due to post-hoc analysis nature. No PFS outcomes were reported.
Rohaan *et al.* (2022)[89]	NCT02278887	RCT	Patients with unresectable metastatic melanoma who had received TIL or ipilimumab following a maximum of one line of prior systemic therapy (excluding ipilimumab)	Patients received zero to one prior LoT Limited overlap in patient key baseline characteristics (ECOG PS and LDH levels) when compared with the lifileucel population
Wilson *et al.* (2021)[87]	NR	Retrospective RWE study	Patients with metastatic melanoma who had received PD-L1 (nivolumab or pembrolizumab) and ipilimumab, either together or sequentially	Small population size (N=11) in the ipilimumab arm Limited baseline characteristics reported
Chemotherapy (N=2)				
Mangin *et al.* (2021)[84]	NR	Retrospective cohort study	Patients with unresectable or metastatic melanoma who had received a first-line treatment by ICI (pembrolizumab, nivolumab, ipilimumab) or BRAF/MEK inhibitors	N/A

Marquez-Rodas *et al.* (2022)[85]	GEM1801	Prospective observational study	Patients with unresectable or metastatic melanoma who had received a second-line treatment with immunotherapy (pembrolizumab, nivolumab, ipilimumab, or other), chemotherapy (including dacarbazine, fotemustine, and others), or targeted therapy (vemurafenib plus cobimetinib, dabrafenib plus trametinib, encorafenib plus binimetinib).	Small population size (N=29) Limited baseline characteristics reported PFS and OS KM curves were reported by BRAF mutation status only, not available for the full study population

Abbreviations: BRAFi, BRAF inhibitor; CTLA4, Cytotoxic T-lymphocyte-associated protein 4; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ICI, Immune checkpoint inhibitor; ITC, Indirect treatment comparison; LDH, Lactate dehydrogenase; LoT, line of treatment; MEKi, Mitogen-activated extracellular signal-regulated kinase inhibitor; N/A, Not applicable; NR, Not reported; PD-(L)1, Programmed death (ligand) 1; RCT, Randomised controlled trial; RWE, Real-world evidence; SLR, Systematic literature review; TIL, Tumour infiltrating lymphocytes.

2.10.2 Selection of the ITC approach

Matching adjusted indirect comparison (MAIC) and simulated treatment comparison (STC) are population-adjusted ITC methods used to estimate the relative effect of treatments when there is a suspected violation of the similarity assumption and they are especially helpful when there is no connected network of evidence between the treatments.[101] Population-adjusted ITCs can adjust for imbalances in study populations to obtain an unbiased estimate of the relative treatment effect.[11] Given the absence of head-to-head trial data and C-144-01 being a single-arm trial, there is a disconnected network of trials comparing lifileucel versus relevant comparators, an unanchored population-adjusted ITC was considered as the most suitable approach. Unanchored population-adjusted ITCs have not previously been used in advanced melanoma in a NICE technology appraisal. However, they have been used in a number of previous cell therapy appraisals.[102,103] The details of both population-adjusted ITC methods, MAIC and STC, are outlined within the NICE Decision Support Unit (DSU) Technical Support Document 18.[104]

An STC was preferred over MAIC approach. The STC approach is a form of outcome regression, applicable where individual patient data (IPD) are available for one population and aggregate data for another. A regression model is fitted to the relevant outcomes, based on the IPD for the intervention and including the covariates that were found clinically relevant and adjustable. Covariate values for the comparator(s) can then be simulated based on the aggregate data reported for these comparator(s), and this is then fed into the regression model to predict the outcomes that would have been observed in the comparator target population.

An STC was preferred over a MAIC approach as there is published evidence to suggest that an STC may provide more accurate estimates than a MAIC where there is poor overlap in baseline characteristics across datasets.[105] In the Centre for Health Technology Evaluation (2020) report developed by Welton *et al.* (2020) to support updates to the NICE evidence synthesis methods, a comparison of unanchored MAIC and STC analysis, found that STC may reduce the variation between observed absolute effects, whereas MAICs may in some circumstances actually increase variation.[106] Furthermore, there were clear differences in key

baseline characteristics of patients in da Silva *et al.* (2021) when compared with the lifileucel C-144-01 population, including ECOG PS and LDH levels of patients at baseline, meaning that the use of an STC will lead to more accurate comparative estimates than a MAIC.

As C-144-01 was a single arm trial, it was not possible to perform an anchored STC. Given this and the absence of head-to-head trial data, an unanchored population-adjusted STC was conducted for lifileucel versus ipilimumab using da Silva *et al.* (2021).[88] Four key assumptions for conducting an unanchored population-adjusted ITC were met, in line with the guidance in NICE DSU Technical Support Document 18:[104]

- Homogeneity of outcomes on each treatment – outcomes on treatment and control are the same whether the individual is assigned to the trial or not. This refers to the trial population and target population in practice.
- Stable unit treatment value – the outcomes of one individual are not affected by any other individuals.
- Conditional constancy of absolute effects – the absolute treatment effects are assumed constant at any given level of the effect modifiers and prognostic variables, and all effect modifiers and prognostic variables are required to be known. This is a far more demanding assumption, and it is widely accepted that it is very hard to meet. For this assumption to be considered sufficient, other assumptions are required. Either the true outcome model does not depend on the correlations between covariates, or the missing correlations in one trial can be imputed from those observed in the second trial.
- Model specification – STC assumes that the outcome model is correctly specified in both prognostic variables and effect modifiers. MAIC weighting models must include all effect modifiers and prognostic variables.

The unanchored population-adjusted STC for lifileucel versus ipilimumab involved three key steps:

1. Cox proportional hazards regression models were fitted to the IPD from C-144-01, incorporating all key treatment effect-modifiers and prognostic variables available in each comparator study.

2. The fitted model was then used to predict survival probabilities and adjusted KM curves for lifileucel in the comparator populations, utilising the aggregate data reported on covariates for the comparator studies.

3. The relative treatment effect was estimated in the form of hazard ratios (HRs) between the lifileucel population from C-144-01 versus the comparators. Standard errors were calculated using a robust estimator. Two HRs and the corresponding standard errors were estimated between the comparator populations and two forms of the lifileucel population, a) using an unadjusted population with no STC applied, and b) using an adjusted, STC, approach, where lifileucel was studied in the same population as ipilimumab and chemotherapy.

2.10.3 Methodology

In the PDAwCS efficacy set of the C-144-01 trial, Cohort 2 comprised of [redacted], while Cohort 4 included [redacted]. Due to the small sample sizes in both cohorts, conducting an ITC analysis upon separate cohorts was considered infeasible. To maximise the sample size for the lifileucel population in the STC analyses, pooled IPD from both cohorts 2 and 4 were used ([redacted]). The demographics and baseline disease characteristics of these patients are presented in Table 7 and Table 8. It was not possible to conduct STC analyses for BRAF V600 positive and negative subgroups, based on sample size in both groups as [redacted] were BRAF positive.

ITC methodologies based on IPD make use of observational or non-randomised IPD.[107] For comparators, published aggregate data were available to inform ipilimumab (da Silva *et al.* [2021][88]) in a population-adjusted indirect comparison, and chemotherapy (Mangin *et al.* [2021][84]) in a naïve, unadjusted comparison versus lifileucel. In the absence of IPD for PFS and OS efficacy endpoints, survival data were reconstructed from published KM curves in da Silva *et al.* (2021) and Mangin *et*

al. (2021), using a validated two-step approach involving curve digitization and the Guyot algorithm.[108] First, published survival curves were digitized using GetData Graph Digitizer®, extracting coordinates to approximate individual event times. The Guyot algorithm was then applied to reconstruct pseudo-IPD by matching the extracted survival probabilities at each time point with the published survival curve data.[108] The rationale for curve digitization and subsequent curve reconstruction is to reconstruct time to event data with its underlying censoring behaviour. This process allowed for the generation of an IPD-based survival curve for ipilimumab and chemotherapy that could be compared consistently to lifileucel.

This method is widely accepted for survival curve reconstruction and has been validated to provide reliable approximations, ensuring a robust and comparable estimate of treatment effects of comparator treatments within the economic model when IPD is unavailable.

Covariate selection

As per the NICE TSD18 recommendation, all prognostic variables and treatment effect modifiers were considered for the propensity score model as these are required to reliably predict absolute outcomes.[104] The identification and selection of prognostic variables and treatment effect modifiers was informed by discussions with UK clinical experts.[109] The following covariates were outlined as important: age, sex, ECOG PS score, LDH levels, target lesion sum diameter and LoT. However, due to data availability and the target lesion sum diameter not being reported in the comparator studies, the following covariates were used in the analysis versus da Silva *et al.* (2021)[88]:

- Age (median),
- Sex (male versus female),
- Disease stage (IIIC versus IV),
- ECOG PS score (0, ≥1),
- LDH levels (normal and ≥ upper limit of normal).

Patient baseline characteristics were available for the lifileucel population from C-144-01 pooled cohorts 2 and 4 (the PDAwCS efficacy set, [redacted]) and the comparator populations from da Silva *et al.* (2021) ipilimumab cohort (N=162) and Mangin *et al*. (2021) ICI-resistant cohort (N=50), as presented in Table 22. However, some patient characteristics were lacking in the published data, which was the main limiting factor.

Table 22: Summary of unadjusted baseline patient and disease characteristics in studies considered for the STC analysis

Characteristic	C-144-01[86] Pooled Cohorts 2 and 4 (N=106)	da Silva et al. (2021)[88] ipilimumab group (N=162)	Mangin et al. (2021)[84] ICI group (N=50)
Age, median (range)	55.2 (20-77)	67.0 (58-74)	68.25 (NR; SD:13.27)
Sex, n (%):			
Male	60 (56.6)	103 (64)	26 (52.0)
Female	46 (43.4)	59 (36)	24 (48.0)
Disease stage, n (%):			
IIIC	10 (9.4)	-	-
IV	96 (90.6)	-	-
III/M1a/M1b	-	44 (27)	-
IIIcd/IVM1ab	-	-	7 (14.0)
M1c	-	118 (73)	23 46.0)
M1d	-		20 (40.0)
ECOG score, n (%):			
0	56 (52.8)	64 (39.5)	16 (39.0)
1	50 (47.2)	88 (54.3)	
≥2	0 (0.00)	7 (4.3)	25 (61.0)
LDH level (U/L), n (%):			
≤ULN/Normal	50 (47.2)	95 (62.5)	10 (23.8)
>ULN	56 (52.8)	57 (37.5)	32 (76.2)
NR	0	10	0
Melanoma subtype, n (%)			
Cutaneous	[redacted]	NR	NR
Mucosal	[redacted]	13 (8.0)	6 (12.0)
Acral	[redacted]	20 (12.3)	6 (12.0)
SSM	[redacted]	49 (30.3)	17 (34.0)
Nodular	[redacted]	27 (16.7)	4 (8.0)
BRAF status, n (%):			

Mutated	[redacted]	34 (21)	0 (0.0)
Wild type	[redacted]	102 (63)	34 (68.0)
Other	[redacted]	26 (16)	14 (28.0)
Unknown	[redacted]	0	2 (4.0)
Metastases, n (%)			
Liver	[redacted]	55 (34.0)	NR
Brain	[redacted]	43 (26.5)	32 (64.0)
Time from last prior anti-PD-(L)1, median (range)	[redacted]	3.0 months (1.0-24.4)	NR

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ICI, Immune checkpoint inhibitors; IRC, Independent review committee; LDH, Lactate dehydrogenase; NR, Not reported; PD-(L)1, Programmed death (ligand) 1; SD, Standard deviation; SSM, Superficial spreading melanoma; STC, Simulated treatment comparison; ULN, upper limit of normal.
Source: C-144-01 clinical pack[86]; da Silva et al. (2021)[88]; Mangin *et al.* (2021)[84]

The reported patient characteristics were considered comparable between C-144-01 and da Silva *et al.* (2021), however, there were some differences in key prognostic factors and treatment effect modifiers. For instance, in da Silva *et al.* (2021), 40% and 54% of patients had an ECOG PS of 0 and 1, respectively, whereas in C-144-01, a [redacted].[86,88] This indicates that patients in C-144-01 were slightly fitter than those in da Silva *et al.* (2021). Hence, as discussed previously, in the absence of strong overlap in baseline characteristics across datasets, the use of an STC approach leads to more accurate model outputs compared to a MAIC approach.

In Mangin *et al.* (2021), there were several key differences in the population characteristics when compared with the C-144-01 population.[84] In particular, there was [redacted]. Given that the baseline characteristics reported in Mangin et al. (2021) did not separate patients by ECOG PS of 0 and 1, it is not possible to adjust for the ECOG status covariate, which represents a significant limitation for a robust population-adjusted indirect comparison versus lifileucel as performance status can be a major driver behind patients' responses to treatments and durability of their survival. UK clinical experts confirmed that ECOG PS is a key prognostic factor and treatment effect modifier, therefore omitting ECOG PS from a potential adjusted analyses would be a significant limitation.[109] Therefore, a naïve, unadjusted comparison using

Mangin *et al.* (2021) was considered the only plausible approach given the data availability.

The characteristics of the lifileucel population from C-144-01 and the ipilimumab population from da Silva *et al.* (2021) used as covariate inputs in the STC analyses are summarised in Table 23.

Table 23: Summary of the covariate data used in the STC for lifileucel versus ipilimumab

Covariate used	C-144-01[86] Pooled Cohorts 2 and 4 (N=106)	da Silva et al. (2021)[88] (N=162)
Age, median	55.2	67.0
Sex, n (%)	Male: 60 (56.6) Female: 46 (43.4)	Male: 103 (64) Female: 59 (36)
Disease stage, n (%)	IIIC: 10 (9.4) IV: 96 (90.6)	III/M1a/M1b: 44 (27) M1c/M1d: 118 (73)
ECOG PS, n (%)	0: 56 (52.8) 1: 50 (47.2)	0: 64 (39.5) ≥1: 95 (58.6)
High LDH levels, n (%)	≤ULN: 50 (47.2) >ULN: 56 (52.8)	Normal: 95 (62.5) >ULN: 57 (37.5) NR: 10

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; LDH, Lactate dehydrogenase; STC, Simulated treatment comparison; ULN, upper limit of normal.
Source: C-144-01 clinical pack[86]; da Silva et al. (2021)[88]

2.10.4 Results for lifileucel versus ipilimumab

2.10.4.1 PFS and OS results

The STC results for PFS and OS in the PDAwCS efficacy set are reported in Table 24. The adjusted and unadjusted HRs for lifileucel versus ipilimumab were estimated using Cox proportional hazards (PH) regression models. For the adjusted analysis, the multivariate Cox PH regression models were fitted to IPD from C-144-01 and applied to ipilimumab population, incorporating all key covariates to account for differences between populations. A statistically significant difference was observed between lifileucel and ipilimumab for both [redacted] endpoints in the unadjusted analysis. A [redacted]

[redacted] endpoints. Figure 12 and

Figure 13 present the KM curves for ipilimumab, and the adjusted and unadjusted curves for lifileucel for PFS and OS, respectively. The estimation of adjusted survival distributions for lifileucel was limited to the duration of available ipilimumab data, which was shorter than the lifileucel follow-up (~20-month versus 48-month follow-up in da Silva *et al.* (2021)[88] and C-144-01, respectively). Due to the absence of longer-term ipilimumab data, adjusted lifileucel curves for both OS and PFS could only be projected up to approximately 44 months. The adjusted lifileucel curves are more conservative as they do not exhibit a plateau, mainly driven by the lack of a plateau in the corresponding ipilimumab OS and PFS curves, with a survival drop observed at the end of the KM curve tails.

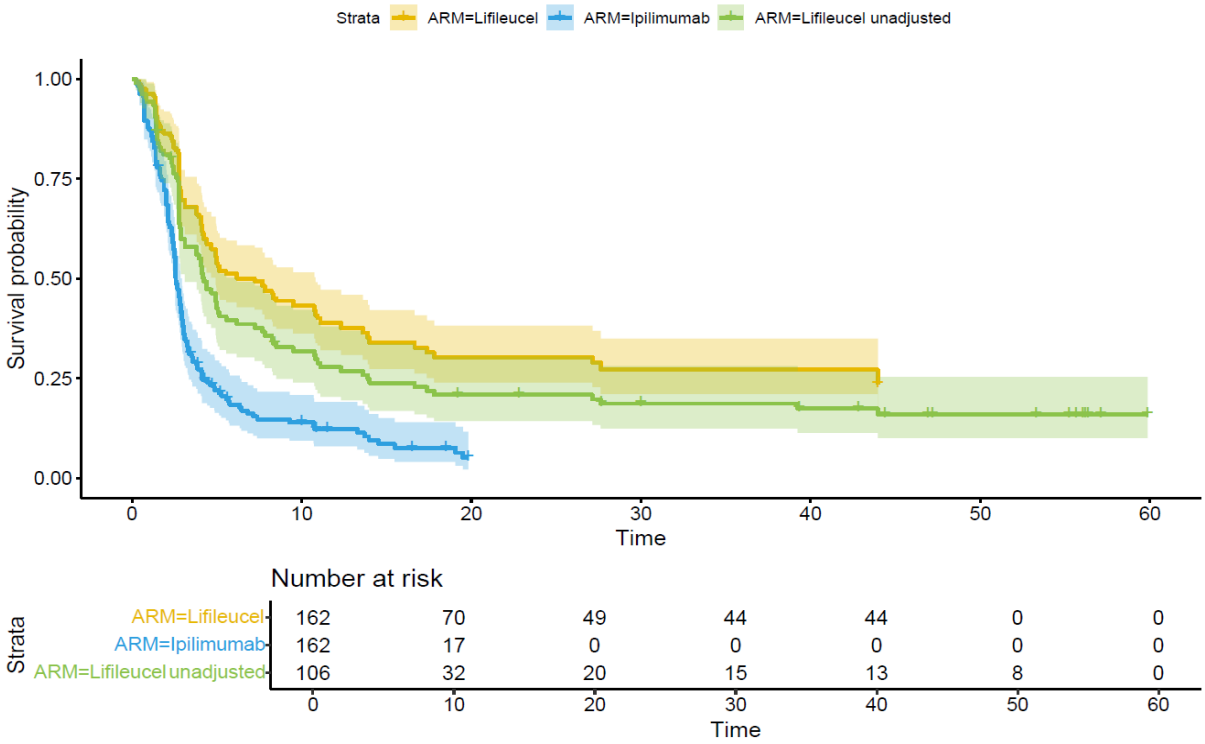
The lifileucel adjusted KM curves [redacted] from the unadjusted KM curves for both PFS and OS. This indicates that patients in the ipilimumab arm had a worse prognosis and/or treatment effect based on the selected covariates, as such, simulating the treatment of lifileucel in patients in the ipilimumab population, improves the survival for lifileucel patients. To explore the impact of each covariate input on the survival outputs, leave-one-out sensitivity analyses were conducted for the selected covariates (see Appendix L for the results of these sensitivity analyses).

Table 24: Summary of STC results for lifileucel versus ipilimumab (PDAwCS efficacy set)

	PFS		OS	
	HR (95%)	p-value	HR (95%)	p-value
Unadjusted	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted	[redacted]	[redacted]	[redacted]	[redacted]

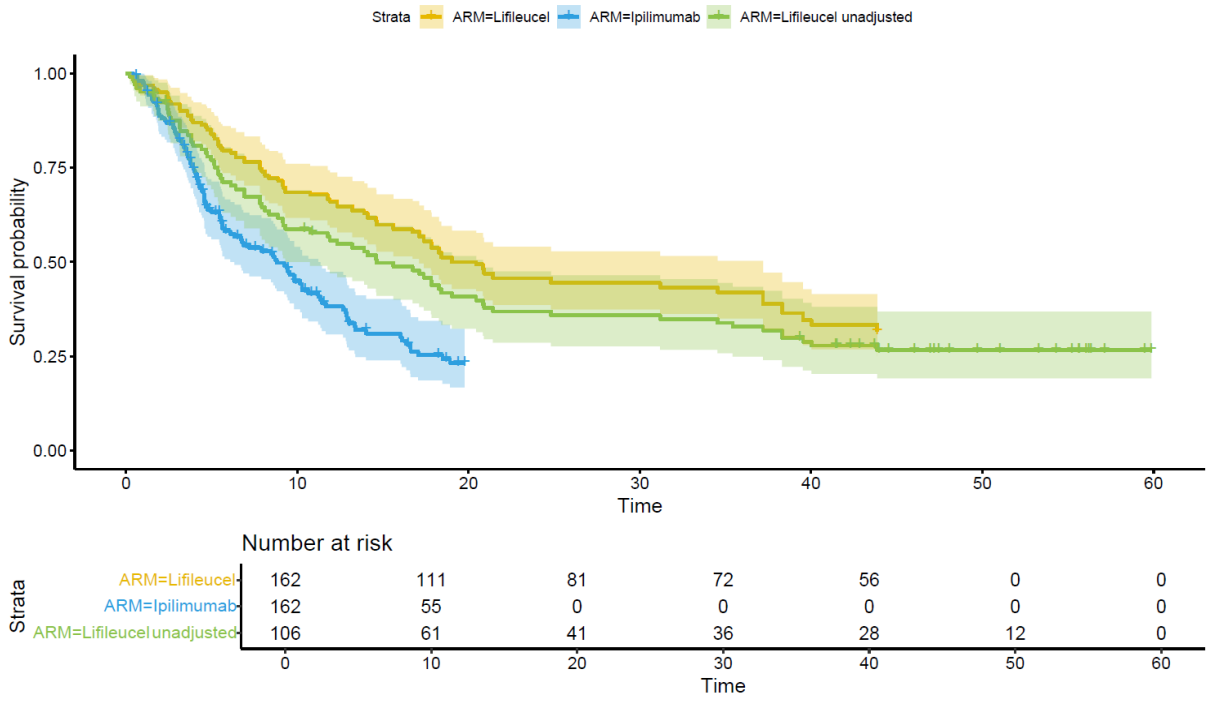
Abbreviations: HR, Hazard ratio; OS, Overall survival; PDAwCS, Pooled data aligned with commercial specifications; PFS, Progression-free survival; STC, Simulated treatment comparison.

Figure 12: Adjusted (STC) and unadjusted KM curves of PFS of lifileucel versus ipilimumab for the PDAwCS efficacy set



Note: The survival probabilities were predicted using the code based on the specified time points. In the code, these time points were set for when there is at least one censored event in the intervention arm, i.e. they are derived from the intervention group's observed event times where there is a censored PFS event to ensure there are patients at risk to estimate survival probabilities. Therefore, the predicted adjusted lifileucel KM curve stops at the last censored PFS event.
The shaded areas around each plot represent 95% confidence intervals.
Abbreviations: Abbreviations: KM, Kaplan-Meier; PDAwCS, Pooled data aligned with commercial specifications; PFS, Progression-free survival; STC, Simulated treatment comparison.

Figure 13: Adjusted (STC) and unadjusted KM curves of OS of lifileucel versus ipilimumab for the PDAwCS efficacy set



Note: The survival probabilities were predicted using the code based on the specified time points. In the code, these time points were set for when there is at least one censored event in the intervention arm, i.e. they are derived from the intervention group's observed event times where there is a censored OS event to ensure there are patients at risk to estimate survival probabilities. Therefore, the predicted adjusted lifileucel KM curve stops at the last censored OS event.
The shaded areas around each plot represent 95% confidence intervals.
The shaded areas around each plot represent 95% confidence intervals.
Abbreviations: KM, Kaplan-Meier; OS, Overall survival; PDAwCS, Pooled data aligned with commercial specifications; STC, Simulated treatment comparison.

Section 2.10.4.2 provides the assessment of proportional hazards for the adjusted, STC, analysis. Whilst the assessment of proportional hazards for the unadjusted analysis is presented in Appendix L.

2.10.4.2 Assessment of proportional hazards (adjusted)

Inspection of the log-cumulative hazards, Schoenfeld residual plot, quantile-quantile (QQ) plot and smoothed hazard rate plots for PFS suggest that the relative hazards for progression are likely to vary over time, and as such, it is not possible to conclude that the proportional hazard (PH) assumption between lifileucel and ipilimumab for PFS holds. See Appendix L which presents the PFS log-cumulative hazards, Schoenfeld residual, QQ and smoothed hazard plots. The respective lines in the log-log plot are relatively parallel and do not intersect, suggesting the PH assumption is held between lifileucel and ipilimumab in the adjusted analysis. Despite a Global

Schoenfeld residual p-value of >0.05, the random pattern and non-zero slope indicate that the PH assumption does not hold. As the PH assumption may not hold it is appropriate to apply different survival approaches and distributions that can model a turning point or changes in hazard rates over time to extrapolate PFS for both treatment arms.

Moreover, in the QQ plot the quantiles do not lie on a straight line, suggesting that the treatment effect is not multiplicative with respect to time. This indicates that the constant accelerated failure time (AFT) assumption is considered to be violated, therefore independent models may be more suitable to extrapolate PFS for both treatment arms.

The hazard for lifileucel increases initially, before decreasing over time, whilst the cumulative hazard for ipilimumab is non-monotonic and diverges from the lifileucel hazard after a certain point, as presented in Appendix L. This means that the hazard of progression for lifileucel patients is less pronounced, while it changes rapidly over the time scale for ipilimumab.

Inspection of the log-cumulative hazards, Schoenfeld residual plot, and the QQ and smoothed hazard rate plots for OS suggest that the relative hazards vary over time, and as such, it is not possible to conclude that the PH assumption for OS holds. See Appendix L which presents the OS log-cumulative hazards, Schoenfeld residual, QQ and hazard rate plots. The respective lines in the log-log plot are not parallel and intersect, reflecting that the PH assumption is violated between lifileucel and ipilimumab in the adjusted analysis. Despite a Global Schoenfeld residual p-value of >0.05, the random pattern and non-zero slope indicate that the PH assumption does not hold. As the PH assumption does not hold it may be appropriate to apply different survival approaches and distributions that can model a turning point or changes in hazard rates over time to extrapolate OS for both treatment arms.

The QQ plot indicates that the quantiles do not lie on a straight line, suggesting that the treatment does not have a multiplicative effect with respect to time, and therefore providing evidence of violation of the constant AFT assumption. Thus, independent models may be more suitable to extrapolate OS for both treatment arms.

The hazard rate for both treatment arms is shown to be non-monotonic, with multiple turning points in the hazard over time, as presented in Appendix L. Notably, the hazard curve for lifileucel exhibits two distinct modes, suggesting that standard parametric distributions may not accurately capture this trend, and it may be more appropriate to use alternative survival distribution approaches such as mixed cure models.

2.10.5 Results for lifileucel versus chemotherapy (unadjusted)

2.10.5.1 PFS and OS results

This section presents the PDAwCS efficacy set PFS and OS results for the naïve, unadjusted analysis using Mangin et al. (2021)[84] data for the chemotherapy arm. The unadjusted HRs for lifileucel versus chemotherapy were estimated using Cox PH regression models, using unadjusted C-144-01 population data without applied covariates. A [redacted] endpoints. Figure 14 and Figure 15 present the PFS and OS KM curves for chemotherapy and unadjusted lifileucel.

Figure 14: Unadjusted KM curves of PFS of lifileucel versus chemotherapy for the PDAwCS efficacy set

[redacted]

The shaded areas around each plot represent 95% confidence intervals.
Abbreviations: KM, Kaplan-Meier; PDAwCS, Pooled data aligned with commercial specifications; PFS, Progression-free survival.

Figure 15: Unadjusted KM curves of OS of lifileucel versus chemotherapy for the PDAwCS efficacy set

[redacted]

The shaded areas around each plot represent 95% confidence intervals.
Abbreviations: KM, Kaplan-Meier; OS, Overall survival; PDAwCS, Pooled data aligned with commercial specifications.

2.10.5.2 Assessment of proportional hazards

Inspection of the log-cumulative hazards, Schoenfeld residual plot, the QQ and smoothed hazard rate plots for PFS suggest that relative hazards are likely to vary over time, and as such, it is not possible to conclude that the PH assumption for PFS

holds. See Appendix L which presents the PFS log-cumulative hazards, Schoenfeld residual, QQ and smoothed hazard plots. The respective lines in the log-log plot are not parallel and intersect, indicating that PH assumption is violated between lifileucel and chemotherapy in the unadjusted analysis. Despite a Global Schoenfeld residual p-value of >0.05, the random pattern and non-zero slope indicate that the PH assumption does not hold. As the PH assumption may not hold it is appropriate to apply different survival modelling approaches and distributions that can model a turning point or changes in hazard rates over time to extrapolate PFS for both treatment arms.

The QQ plot indicates that the quantiles do not lie on a straight line, suggesting that the treatment effect is not multiplicative with respect to time, and therefore providing evidence of violation of the constant AFT assumption. Thus, independent models may be more suitable to extrapolate PFS for both treatment arms.

The hazard for lifileucel increases initially, before decreasing over the time scale, whilst the cumulative hazard for chemotherapy is non-monotonic and diverges from the lifileucel hazard after a certain point. This means that the hazard of progression decreases for lifileucel patients over time while it changes rapidly over the time scale for chemotherapy.

Inspection of the log-cumulative hazards, Schoenfeld residual plot, the QQ and smoothed hazard rate plots for OS suggest that relative hazards are likely to vary over time, and as such, it is not possible to conclude that the PH assumption for OS holds. See Appendix L which presents the PFS log-cumulative hazards, Schoenfeld residual, QQ and smoothed hazard plots. The respective lines in the log-log plot are not consistently parallel and intersect, indicating that the PH assumption is violated between lifileucel and chemotherapy in the unadjusted analysis. Despite a Global Schoenfeld residual p-value of >0.05, the random pattern and non-zero slope indicate that the PH assumption does not hold. As the PH assumption does not hold it is appropriate to apply different survival approaches and distributions that can model a turning point or changes in hazard rates over time to extrapolate OS for both treatment arms.

The QQ plot indicates that the quantiles do not lie on a straight line, suggesting that the treatment effect is multiplicative with respect to time, and therefore providing evidence of violation of the constant AFT assumption. This indicates that independent models may be more suitable to extrapolate OS for both treatment arms.

The hazard for unadjusted lifileucel is shown to be monotonically decreasing, whilst it is non-monotonic for chemotherapy and diverges from the lifileucel hazard after a certain point. This means that the hazard of progression decreases for lifileucel patients over time while it changes rapidly over the time scale for chemotherapy.

2.10.6 Limitations of the ITC

An SLR, supplemented by "grey" literature searches, was conducted to identify all relevant publications reporting clinical outcomes for patients with untreated unresectable or metastatic melanoma (Stage IIIc, IIId or IV) treated with ipilimumab, chemotherapy, or BSC. However, upon initial assessment, most studies did not meet the inclusion criteria for the ITC, primarily due to either patient population not aligning with the lifileucel anticipated license (lack of data for patients post anti-PD-1), absence of published KM curves. Following a full assessment of studies, only two studies for ipilimumab (N=1) and chemotherapy (N=1) were deemed suitable to be used in the ITC versus lifileucel.

The main issues faced in the ITC were differences in the study designs and a lack of reported data, which may introduce uncertainty into the analysis outcomes. As part of the feasibility assessment for the population-adjusted ITC, the risk of bias inherent within the study designs and patient characteristics were considered for each study.

- A substantial limitation for the ITC for lifileucel versus chemotherapy is the small sample size in Mangin *et al*. (2021) (N=50), meaning that a robust STC is not possible.[84]

- The data maturity varied across the datasets, with the C-144-01 having the longest duration of study follow-up of 45.6 months. In da Silva *et al*. (2021), the duration of follow-up was 22.1 months.[88] In Mangin *et al*. (2021), the mortality

events were only reported up to 12 months.[84] While the median PFS and OS was met in all three datasets, the differences in follow-up mean that there is uncertainty in the long-term relative treatment effect of lifileucel versus ipilimumab and chemotherapy.

- The inclusion criteria in Mangin *et al*. (2021) outline that all patients must have received one prior line with ICI, however PFS and OS KM data are not reported for patients who have received anti-PD-(L)1 only.[84] As such the combined prior-ICI (anti-PD-(L)1 and anti-CTLA-1) patients are not completely aligned with the lifileucel anticipated license, which may introduce unquantifiable bias into the ITC outcomes.

- While Mangin *et al.* (2021) reported some information on ECOG PS, it did not differentiate between patients with ECOG PS of 0 and 1, meaning that this key prognostic factor could not be adjusted for in the ITC for lifileucel versus chemotherapy, a significant limitation for developing a robust ITC.[84]

The important prognostic factor or treatment effect modifier, target lesion sum of diameter, was not reported in either da Silva *et al*. (2021) or Mangin *et al*. (2021), meaning this characteristic could not be adjusted for in the ITC. [88,84]

2.11 Adverse reactions

The safety and tolerability of lifileucel for the treatment of adult patients with unresectable or metastatic melanoma treated with ≥1 systemic prior therapy including a PD-1-blocking antibody and, if BRAF V600 mutation-positive, a BRAF/MEK inhibitor was evaluated as a secondary outcome in the C-144-01 study.[86]

The analysis of the safety population involved the TH set, which included all patients who had a tumour resected for the production of lifileucel, and the SAS set, which included all patients who received any lifileucel infusion. As mentioned in Section 2.4.1, the safety outcomes based on the SAS are used in the model. Safety outcomes by study period, as well as exposure to lifileucel are presented in Appendix D.

This analysis primarily focused on the proportion of patients reporting AEs, SAEs and deaths. AEs were recorded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0. The severity of AEs was graded by the Investigator using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

A summary of post-treatment-emergent AEs reported at an incidence of ≥5% in the C-144-01 study are presented in Table 25.

In Pooled Cohorts 2 and 4, the percentage of patients who experienced at least 1 AE and at least 1 Grade 3/4 AE was, as expected, [redacted] had their lifileucel infusion prematurely discontinued due to a TEAE.

More patients experienced at least one SAE during the treatment-emergent period [redacted] However, only [redacted] were reported as directly related to lifileucel itself, which suggests that lifileucel is safe and generally well-tolerated. During the post-treatment-emergent period, [redacted] of the patients experienced at least 1 AE, [redacted] experienced at least 1 Grade 3/4 AE, and [redacted] experienced at least 1 SAE. The TEAE profile was consistent with underlying disease and known safety profiles of LD and IL-2 regimens.[94] There were [redacted] that resulted in death reported during the TH period, [redacted] during the LD period, [redacted] during treatment-emergent period, and [redacted] during the post-treatment-emergent period.

During the 4-year study follow-up for Pooled Cohorts 2 and 4, the most common post-treatment-emergent AEs with an incidence of ≥5% were [redacted] (see Table 25 for more details). The manageable profile of these AEs, combined with their relatively low incidence rates, supports the treatment's overall tolerability.

Most TEAEs were anticipated and manageable, and as presented in Appendix D, TEAEs in Pooled Cohorts 2 and 4 [redacted] and improving QoL as they continue treatment (further detailed in Section 2.6.4).

2.11.1 Treatment-emergent adverse events

A summary of the most common TEAEs, with an incidence of 20% or higher, are presented in Table 26. The most common AEs reported for any grade are [redacted][86] The most common AEs reported for Grade 3/4 are [redacted]

Table 25: Post-treatment-emergent AEs reported at an incidence of ≥5% for the SAS

System Organ Class preferred Term	Cohort 4 (N=89)			Cohort 2 (N=67)			Pooled Cohorts 2 and 4 (N=156)		
	Any grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)	Any grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)	Any grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)
Blood and lymphatic system disorders									
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lymphopenia[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders									
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions									
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations									
Sepsis[e]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders									
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders									
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Renal and urinary disorders									
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders									
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a AE grouped terms of platelet count decreased and thrombocytopenia.
c AE grouped terms of white blood cell count decreased and leukopenia.
d AE grouped terms of lymphocyte count decreased and lymphopenia.
e A Grade 5 sepsis was reported in a Cohort 2 patient; the cause of death in this patient was metastatic melanoma complicated by sepsis. Thus, a Grade 5 sepsis event is displayed in AE tables, but this patient was reported as having died of PD in the death section of this CSR.
Notes: AEs are coded based on MedDRA version 24.0. Grades are based on CTCAE version 4.03.
Patients with multiple events for a given PT are counted only once using the maximum grade under each PT.
AEs are sorted by decreasing frequency of SOC, and of PT within SOC per any grade in the Pooled Cohorts 2 and 4 group.
Post treatment-emergent AEs refer to AEs that started 30 days post lifileucel infusion and through 6 months after the lifileucel infusion or up to the start of a new anti-cancer therapy, whichever occurred first.
Abbreviations: AE, adverse event; CSR, clinical study report; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; PD, progressive disease; PT, Preferred Term; SOC, System Organ Class.
Source: C-144-01 clinical pack[86]
DCO: 30Jun2023

Table 26: Most common TEAEs reported at an incidence of ≥ 20% of patients for the SAS

System Organ Class Preferred Term	Cohort 4 (N=89)		Cohort 2 (N=67)		Pooled Cohorts 2 and 4 (N=156)	
	Any Grade n (%)	Grade 3/4 n (%)	Any Grade n (%)	Grade 3/4 n (%)	Any Grade n (%)	Grade 3/4 n (%)
Blood and lymphatic system disorders						
Thrombocytopenia[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lymphopenia[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders						
Tachycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders						
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions						
Chills	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigations						

Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders						
Hypophosphatemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders						
Hypoxia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders						
Rash	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alopecia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders						
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: AEs are coded based on MedDRA version 24.0. Grades are based on CTCAE version 4.03. Patients with multiple events for a given PT are counted only once using the maximum grade under each PT. AEs are sorted by decreasing frequency of SOC, and of PT within SOC per any grade in the Pooled Cohorts 2 and 4 group. TEAEs include all AEs that began starting from the lifileucel infusion to 30 days post lifileucel infusion.
a AE grouped terms of platelet count decreased and thrombocytopenia
b AE grouped terms of neutrophil count decreased and neutropenia
c AE grouped terms of white blood cell count decreased and leukopenia
d AE grouped terms of lymphocyte count decreased and lymphopenia
Abbreviations: AE, Adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred term; SAS, Safety analysis set; SOC, System Organ Class; TEAE, Treatment-emergent adverse event.
Source: C-144-01 clinical pack[86]
DCO: 30June2023

2.11.2 Deaths

Of the [redacted] (12.7%) died after the tumour harvest and did not receive the lifileucel infusion with the primary cause of death [redacted][86] Of these [redacted] patients:

- [redacted] did not receive any component of the lifileucel treatment regimen due to either a decline in clinical status, TIL not being available, the patient not meeting requirements to receive TIL, withdrawal of consent or the patient dying during the survival follow-up period
- [redacted] began the LD preparative regimen but did not receive lifileucel due to AEs
- [redacted] died due to SAEs during the LD preparative regimen administration

The deaths that occurred after the lifileucel infusion (both within and post 30 days) are summarised in Appendix D. With a median study follow-up of 48.1 months, [redacted] of patients died following the lifileucel infusion.[86] Of these, [redacted] occurred within 30 days following the lifileucel infusion with [redacted] primarily attributed to PD and [redacted] to an AE. Only [redacted] was related to all components of the lifileucel regimen (LD, lifileucel and IL-2). The others were related to other components of the lifileucel regimen excluding the lifileucel infusion.

The remaining [redacted] occurred post 30 days following the lifileucel infusion with [redacted] attributed to progressive disease.[86] [redacted] were related to AEs with only [redacted] being related to all components of the lifileucel regimen. The cause of the remaining [redacted]

2.11.3 Safety overview

Table 27 provides a summary of the AEs in the SAS. Values are high for patients with at least one AE, Grade 3/4 AEs and SAEs when looking at the lifileucel treatment regimen as a whole.[86] Although lifileucel is administered as a part of treatment regimen, the SAEs are much lower when looking at lifileucel-related AEs only. Low SAEs related to lifileucel only ([redacted] suggest lifileucel is well-tolerated. The

most common AEs reported for Grade 3/4 with an incidence of equal to or greater than 20% are [redacted]

Table 27: Summary of AEs for the SAS

	Cohort 4 (N=89), n (%)	Cohort 2 (N=67), n (%)	Pooled Cohorts 2 and 4 (N=156), n (%)
Patients with at least 1 AE [a]	[redacted]	[redacted]	[redacted]
Patients with at least 1 AE related to lifileucel only[b]	[redacted]	[redacted]	[redacted]
Grade 3+ AE[a,c]	[redacted]	[redacted]	[redacted]
Grade 3+ AE related to lifileucel only[b,c]	[redacted]	[redacted]	[redacted]
SAE[a]	[redacted]	[redacted]	[redacted]
SAE related to lifileucel only[b]	[redacted]	[redacted]	[redacted]
AEs leading to death[d]	[redacted]	[redacted]	[redacted]
AEs leading to study drug discontinuation	[redacted]	[redacted]	[redacted]

a Related to lifileucel regardless of a relationship to other components of the treatment regimen (i.e. cyclophosphamide, fludarabine or IL-2).
b Related to lifileucel only (any grade) and not related to other components of the treatment regimen (i.e. cyclophosphamide, fludarabine or IL-2)
c No Grade 5+ AEs related to lifileucel only were reported
infusion to .
Abbreviations: AE, Adverse event; IL-2, Interleukin-2; SAE, Serious adverse event; SAS, Safety analysis set.
Source: C-144-01 clinical pack[86]
DCO: 30June2023

2.12 Ongoing studies

No additional studies are planned in the population of interest.

2.13 Interpretation of clinical effectiveness and safety evidence

Despite significant advances in the treatment landscape for patients with untreated unresectable or metastatic melanoma over the past decade, a considerable proportion of patients do not respond to existing therapies or eventually relapse.[58] Hence, there is a substantial unmet need for an efficacious treatment for patients with advanced melanoma following progression on ICIs at second line and beyond.[58]

Lifileucel meets this need demonstrating clinically meaningful benefits, tolerable safety profile, and minimising the likelihood of relapse in this population.

Lifileucel is a one-time, first-in-class, ACT specifically utilising the patients' own cells. Although TILs naturally target tumours, they are often insufficient or under-activated. By isolating and amplifying these cells, lifileucel enhances the body's anti-tumour response.

TILs are first harvested and then sent to a specialised laboratory for expansion. Over several weeks, the TILs multiply into billions, creating a robust population capable of targeting and destroying cancer cells.[2] Once the expanded TILs are reintroduced back into the patient, these personalised immune cells target cancer by recognising specific antigens on tumour cells presented via major histocompatibility complex (MHC) molecules. Binding to these antigens triggers a cytotoxic response, where the TILs release perforins and granzymes to destroy the cancer cells. This tailored approach harnesses the patient's own immune system, offering a highly individualised and bespoke treatment designed to effectively combat their cancer.

Lifileucel's efficacy lies in its ability to target multiple antigens on tumour cells, a distinct advantage over therapies that focus on a single antigen and risk tumour escape through mutation. By using the patient's own TILs, lifileucel also minimises the risk of adverse immune reactions, such as graft-versus-host disease, associated with other cell-based therapies.

The C-144-01 trial, provides direct evidence to demonstrate the efficacy and safety of lifileucel in adults patients with advanced melanoma irrespective of their BRAF mutation status and for patients who have not responded to other treatments.[86] This is pertinent given the limited subsequent treatment options patients face following disease progression, with the limited options indicating subpar benefits to patients' outcomes. The observed ORR of [redacted] for the PDAwCS efficacy set highlights the potential of lifileucel to enhance response rates of heavily pretreated patients with Stage IIIc-IV melanoma. With a median follow-up of 47.4 months, lifileucel achieved a median OS of [redacted] and a median PFS of [redacted]--. The durable efficacy of lifileucel is further underscored by a 12-month OS

rate of -[redacted], with [redacted] surviving at least four years. The meaningful responses and the extended survival, including an extended period without disease progression, supports improved QoL outcomes for patients. It also demonstrates lifileucel's curative potential which is exceptionally rare for such an advanced stage of cancer as there are currently no curative treatments for Stage IIIc-IV melanoma.

As there are currently no head-to-head data available for the comparison of lifileucel versus relevant comparators in patients with pretreated, unresectable or metastatic melanoma, an unanchored population-adjusted STC assessing the comparative effectiveness of lifileucel versus ipilimumab was conducted. As the only relevant source identified to inform the chemotherapy population (Mangin *et al.* [2021][84]) had substantial limitations related to the small sample size and limited patient data reported, it was deemed unfeasible to conduct a robust STC for lifileucel versus chemotherapy. Despite the inherent limitations of a naïve, unadjusted analysis versus chemotherapy, it is the most relevant comparison available for lifileucel, therefore the results of this analysis were presented for transparency.

The results of the STC analyses conducted using the PDAwCS efficacy set demonstrated that [redacted]. The analysis conducted was based on the best available data to date and aligned with the guidance provided by the NICE DSU for population adjusted comparisons.[104] The UK clinical experts at a clinical advisory board (October 2024) had no concerns regarding the covariate selection and STC outputs.[16]

Lifileucel provides the only potentially curative treatment options for patients who have a high unmet need, with limited long-term survival potential. Not only has lifileucel demonstrated impressive clinical benefits and a manageable safety profile, the hope that this treatment provides should not be underestimated. Furthermore, given its' mode of action of a single infusion not only benefits the patients themselves, but also has key benefits to their careers, the health system and society overall.

3 Cost-effectiveness

3.1 Published cost-effectiveness studies

An SLR was undertaken in August 2024 and updated in January 2025 to identify published cost-effectiveness studies and public NICE appraisals relevant to the decision problem, for the treatment of adult patients with unresectable or metastatic previously treated melanoma to support the development of the CEA. Searches were limited from 2014 onwards to capture publications post the introduction of PD-1s in melanoma, ensuring only publications concerning the relevant treatment landscape and patient population were considered. The methods, search strategies and inclusion and exclusion criteria used, along with results of the SLR and quality assessments of qualifying cost-effectiveness studies are provided in Appendix E.

A total of 154 records were identified from Embase. A total of 104 records were excluded following screening of title and abstract. The remaining 50 records were selected for full-text review. At full-text review, 47 studies were excluded: four based on intervention/comparators, 15 based on population and 28 based on study type and outcomes. Overall, three studies were selected for data extraction. Finally, through a “grey” literature search one further study was selected for data extraction, alongside 12 previous NICE TAs in advanced melanoma, five previous NICE TAs for CAR Ts, a total of 21 records were selected for data extraction. Of the 21 records, all were economic evaluations from various local perspectives. Two studies were conducted in the Netherlands, one in Japan, one in the US and 17 from the UK (NICE TAs). A summary of the published cost-effectiveness studies and previous melanoma TAs extracted are presented in Table 28 below, the CAR T TAs in Appendix E, Section E.6 Table 22, and a PRISMA diagram detailing screening of papers is shown in Appendix E.

Table 28: Summary of extracted cost-effectiveness papers and previous TAs identified in the economic SLR (n=16)

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Published studies						
Retèl *et al.* (2018)[110] (Netherlands)	2018	A three-state Markov model (stable disease [responders], PD and death) over a 10-year time horizon.	Previously treated metastatic melanoma (stage IV) was simulated, at a starting age of 52 years. Specific previous treatment not listed.	• Ipilimumab QALYs 0.38 • TIL QALYs 0.45	• Total ipilimumab cost €94,705 • TIL total cost €81,140 • Future costs were discounted by 4% per year.	TIL dominant versus ipilimumab
ten Ham *et al.* (2024)[111] (Netherlands)	2024	A Markov model with health states of PF PD, and death, over a lifetime horizon.	Patients with unresectable stage IIIC–IV melanoma after failing first-line treatment with nivolumab or pembrolizumab or 2L treatment with BRAF/MEK inhibitors for patients with *BRAF* mutations. Median (range) age, years: • TIL: 59 (26-74) • Ipilimumab: 59 (30-77) • Total: 59 (66-77)	• Undiscounted ipilimumab total QALYs: 2.46 • Discounted ipilimumab: total QALYs: 2.28 • Undiscounted TIL-NKI/CCIT total QALYs: 3.52 • Discounted TIL-NKI/CCIT: total QALYs 3.22	• Undiscounted ipilimumab total costs €433,634 • Discounted ipilimumab total costs: €365,068 • Undiscounted TIL-NKI/CCIT total costs €347,168 • Discounted TIL-NKI/CCIT total costs: €292,369	TIL-NKI/CCIT dominant versus ipilimumab

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Paly *et al.* (2020)[112] (Japan)	2020	A three-state model with PSM approach. Health states included pre-progression, post-progression, and death, over a 30-year (lifetime) horizon.	Eligible patients included those from the Checkmate 067 trial with previously untreated, unresectable, or metastatic histologically confirmed stage III or stage IV melanoma. The model used OS and PFS projection over a 30-year time horizon, representative of a lifetime time horizon for a population with a starting age of approximately 60 years.	• Nivolumab + Ipilimumab: 7.7 • Nivolumab: 6.2 • Ipilimumab: 2.8	• Nivolumab + Ipilimumab: ¥19,664,847 • Nivolumab: ¥18,501,011 • Ipilimumab: ¥11,899,588	Base-case ICER (¥/LY): Nivolumab + ipilimumab versus: • Nivolumab: ¥628,278 • Ipilimumab: ¥1,263,895 Nivolumab versus: • Ipilimumab: ¥1,538,260 ICER (¥): Nivolumab + ipilimumab versus: • Nivolumab: ¥777,911 • Ipilimumab: ¥1,583,787 Nivolumab versus: • Ipilimumab: ¥1,937,683

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Curl *et al.* (2014)[113] (US)	2014	A deterministic expected-value cost-utility model, with a decision tree structure used over a lifetime horizon.	BRAF-mutated metastatic or unresectable melanoma patients. An average age of 50 was assumed.	• Dacarbazine: 0.30 • Vemurafenib: 0.72 • Vemurafenib + ipilimumab: 1.34	• Dacarbazine: $8,391 • Vemurafenib: $156,831 • Vemurafenib + ipilimumab: $254,695	ICER for dacarbazine only versus: • Vemurafenib only: $353,993 • Vemurafenib + ipilimumab: $158,139
Previous TAs						
TA268[77]	2012	PSM with four health states: • Baseline disease • Non-progressive disease • Progressive disease Death	Advanced (unresectable or metastatic) melanoma in people who have received prior therapy. The average age of population was 55.6 years	Incremental QALY: 1.37	Incremental cost: £83,351	Ipilimumab versus BSC: £60,737
TA269[68]	2012	Three-state PSM: • Progression-free • Post-progression Death	Advanced (unresectable or metastatic) melanoma in people who have received prior therapy. Average age of patients: • Vemurafenib: 56.0 years	ND*	ND*	Vemurafenib versus dacarbazine: £56,410

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
			• Dacarbazine: 52.0 years			
TA319[74]	2014	Semi-Markov PSM	Adults with previously untreated advanced (unresectable or metastatic) melanoma. Median age of CA184-024 patients on ipilimumab + DTIC: 57.5 years	• Ipilimumab: 2.31 • Dacarbazine: 1.56 • Vemurafenib: 2.13	• Ipilimumab: £68,416 • Dacarbazine: £44,267 • Vemurafenib: £80,658	• Ipilimumab versus dacarbazine: £31,559 • Vemurafenib versus dacarbazine: £63,534
TA321[69]	2014	Three-state PSM: • Progression-free • Post-progression • Death	Unresectable or metastatic BRAF V600 mutation positive melanoma. Average age of patients: • Dabrafenib: 53.5 years • Dacarbazine: 51.6 years	ND*	ND*	Dabrafenib versus dacarbazine: £49,019
TA357[70]	2015	PSM with three health states: • Pre-progression • Post-progression • Death	Advanced (unresectable or metastatic) melanoma in adults only: after the disease has progressed with ipilimumab and, for	• Pembrolizumab: 2.26 • BSC: 1.07	Total cost pembrolizumab: £53,698 Total cost BSC: £15,960	Pembrolizumab versus BSC: £31,764

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
			BRAF V600 mutation positive disease, a BRAF or MEK inhibitor. Average age of patients: • Pembrolizumab 2mg/kg: 62.0 years • Pembrolizumab 10mg/kg: 60.0 years • Chemotherapy: 63.0 years			
TA366[71]	2015	PSM with three health states: • Pre-progression • Post-progression • Death	Advanced (unresectable or metastatic) melanoma that has not been previously treated with ipilimumab, in adults. Average age of patients: • Pembrolizumab Q2W 10mg/kg: 61.0 years • Pembrolizumab Q3W 10mg/kg: 63.0 years • Ipilimumab 3mg/kg Q3W: 62.0 years	• Pembrolizumab: 3.14 • Dabrafenib: 2.17 • Vemurafenib: 1.73 • Ipilimumab: 2.69	• Pembrolizumab: £76,689 • Dabrafenib: £71,029 • Vemurafenib: £83,384 • Ipilimumab: £97,873 •	Pembrolizumab versus dabrafenib: £5,852

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
TA384[78]	2016	Semi-Markov model with three health states: • Pre-progression • Progression • Death	Advanced (unresectable or metastatic) melanoma in adults. Average age of patients: • BRAF mutation negative: 63.0 years • BRAf mutation positive: 56.0 years	• Nivolumab (BRAF-negative): 4.31 • Nivolumab (BRAF-positive): 4.27	ND*	• Nivolumab versus dacarbazine: £23,583 • Nivolumab versus ipilimumab: £7,346
TA400[73]	2016	Semi-Markov model with three health states: • Pre-progression • Progression • Death	Advanced (unresectable or metastatic) melanoma in adults. Average age of patients: • Nivolumab + ipilimumab: 59.3 years • Ipilimumab: 60.8 years	ND*	ND*	Nivolumab with ipilimumab versus ipilimumab alone: £10,433
TA396[76]	2016	Three-state PSM: • PFS • PPS • Death	Unresectable or metastatic melanoma in adults with a BRAF V600 mutation. Average age of patients: • Trametinib + dabrafenib: 55.1 • Dabrafenib: 55.3	• Dabrafenib: 2.15 • Vemurafenib: 2.10 • Trametinib + dabrafenib: 3.44	• Vemurafenib incremental cost: £5,351 • Trametinib+dabrafenib incremental cost: £129,707	Trametinib with dabrafenib versus dacarbazine: £49,804

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
TA410[114]	2016	Three-state PSM: • Non-progressive disease • Progressive disease • Death	Unresectable, regionally or distantly metastatic (stage 3B, 3C or 4M1a) melanoma that has not spread to bone, brain, lung or other internal organs, only if treatment with systemically administered immunotherapies is not considered the best option by a multidisciplinary team. Average age of patients: 62.0 years	ND	ND	• Talimogene laherparepvec versus dacarbazine: £23,919 • Talimogene laherparepvec versus BSC: £24,094
TA562[75]	2019	PSM with three health states: • Progression-free • Post-progression • Death	Unresectable or metastatic BRAF V600 mutation-positive melanoma in adults. Average age of patients: 55.3 years.	Encorafenib + Binimetinib versus Dabrafenib + trametinib (incremental): 0.453	ND	ND
TA950[115]	2024	Three-state PSM: • Progression-free • Progressed disease • Death	Advanced (unresectable or metastatic) melanoma in people 12 years and over, only if nivolumab-relatlimab is stopped	ND	ND	• Nivolumab-relatlimab versus

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
			after 2 years of treatment, or earlier if the cancer progresses. Average age of patients: • Nivolumab + relatlimab: 63.0 years • Nivolumab: 62.0 years			nivolumab: £87,582 • Nivolumab-relatlimab versus nivolumab-ipilimumab: £148,869 • Nivolumab-relatlimab versus pembrolizumab: £43,670

Abbreviations: BSC, Best supportive care; ICER, Incremental cost-effectiveness ratio; MEK, Mitogen-activated protein kinase; ND, Not disclosed; PD, Progressive disease; PF, Progression-free; PFS, Progression-free survival; PPS, Post-progression survival; PSM, Partitioned survival model; QALY, Quality-adjusted life year; TA, Technology appraisal.
* ND indicates instances where information was redacted in TAs.

3.2 Economic analysis

No cost-effectiveness models assessing the economic value of lifileucel were identified in the SLR. Thus, a *de novo* model was constructed using Microsoft Excel® to assess the cost-effectiveness of lifileucel in the treatment of adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor.

The model structure and inputs were informed by a review of existing technology appraisals (TAs) in metastatic unresectable melanoma, the availability of data from the C-144-01 trial and UK clinical experts opinion.[16,70,71,74,77,78,86] Previous CAR-T NICE TAs were also reviewed due to key similarities between CAR-T and lifileucel mechanism of actions and drug delivery systems, involving personalised and cell-based delivery approaches and due to curative potential of both treatment modalities.[116–121] The partitioned survival model (PSM) structure was selected for the economic analysis due to availability of relevant data (i.e. PFS and OS survival curves), along with other considerations. More details regarding the model structure and rationale can be found in Section 3.2.2.3.

3.2.1 Patient population

The patient population considered in this economic analysis is in line with the C-144-01 trial, the final scope, the decision problem and the anticipated UK licensed indication for lifileucel (as detailed in Section 1.2).[86]

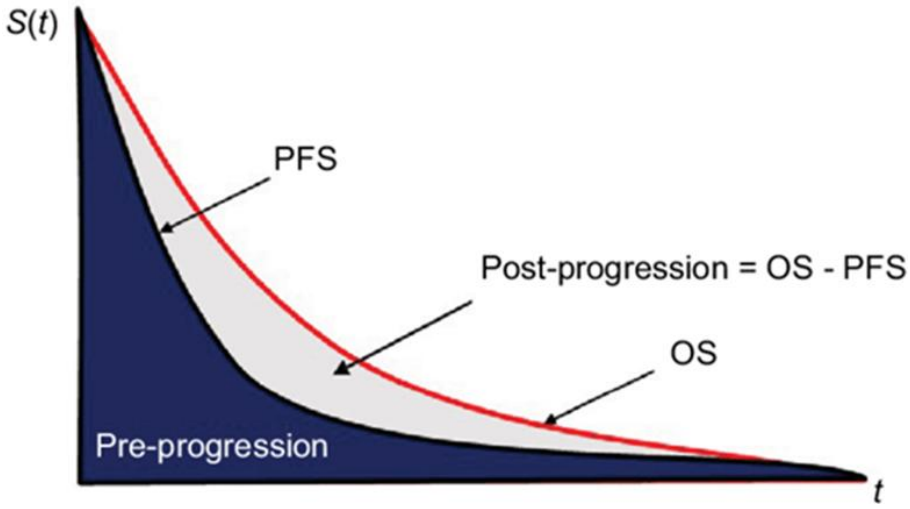
The baseline characteristics of the patient population were informed by the C-144-01 trial and are generalisable to the UK population, as confirmed by UK clinicians.[16,86] As described in Section 2.3.1, baseline characteristics of Cohorts 2 and 4 (PDAwCS efficacy set) from C-144-01 clinical trial were used in the model, since patients in these cohorts had a single treatment of cryopreserved lifileucel which aligned with the anticipated UK licence. The baseline characteristics are summarised in Table 7, Section 2.3.3.

3.2.2 Model structure

3.2.2.1 Partitioned survival model

The cost-effectiveness analysis (CEA) uses a PSM structure with three mutually exclusive health states: progression-free (PF), progressed disease (PD), and death, as illustrated in Figure 16. The PSM structure and health states considered in this analysis are aligned with numerous NICE appraisals for metastatic melanoma, described in further detail in Section 3.2.2.6.

Figure 16: Health state structure used in the economic model



Abbreviations: OS, Overall survival, PD, Progressed disease; PFS, Progression-free survival.

3.2.2.2 Health states and transitions

In a PSM, health state occupancy is determined by allocating the proportion of patients alive into PF and PD health states at discrete time points, based on extrapolated progression-free survival (PFS) and overall survival (OS) data.

Health states are independent of each other and mutually exclusive, with the proportion of patients dynamically changing at each model cycle. The transitions in the model are also irreversible. This approach reflects that once patients experience disease progression, they cannot move back to a pre-progression state. Figure 17 illustrates how health state occupancy is determined:

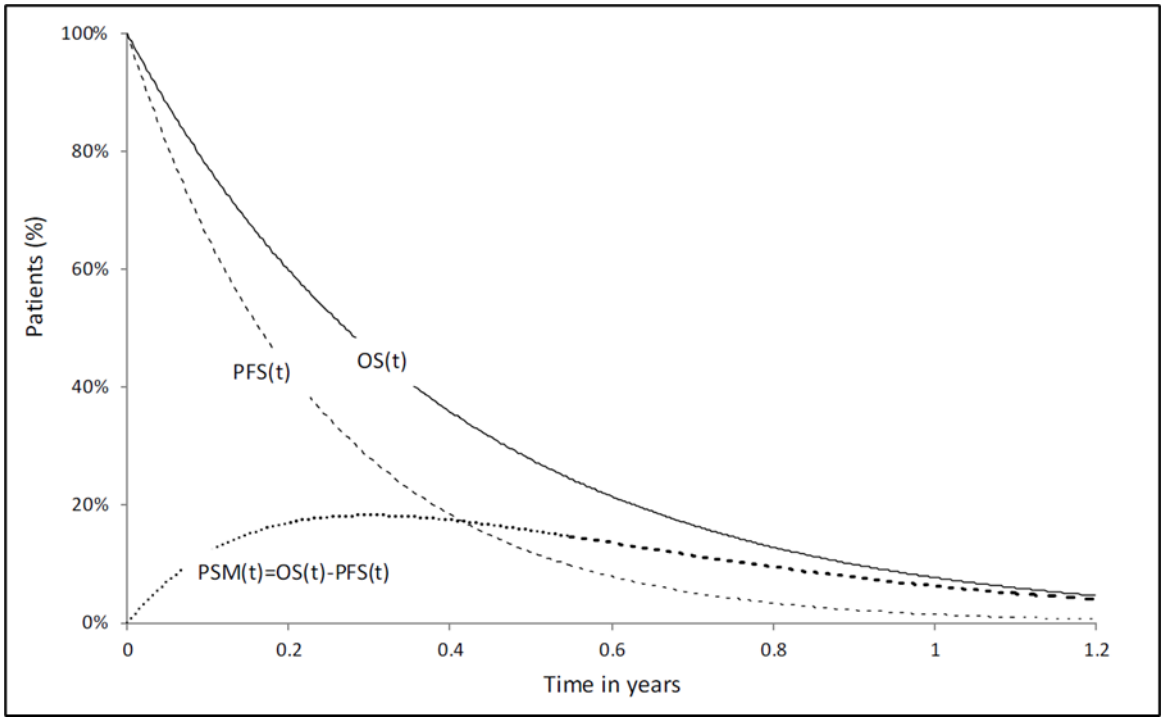
- **PF**: The proportion of patients who are in the PF health state is derived directly from the modelled PFS(t) curves for each treatment. Patients enter the model

in the PF health state, receiving either lifileucel or one of the comparator treatments; ipilimumab or chemotherapy or BSC. Patients in the PF health states are constrained by the OS(t) so that the number of PF patients does not exceed the total number of patients alive, as this would be clinically implausible. From the PF health state, patients may remain there or transition to other health states: PD or death.

- **PD**: The PD health state captures patients who have experienced disease progression. Patients remain in this state until transitioning to death. The proportion of patients in the PD health state is calculated as the difference between modelled OS(t) and PFS(t) curves, representing all alive patients who are no longer in the PF health state.

- **Death**: Death is an absorbing health state; patients cannot transition back to PF or PD health states once they die and enter this health state. Mortality rates are calculated as 1-OS(t). OS(t) is constrained by age- and gender-matched UK general population mortality to ensure that the modelled all-cause risk of death based on trial's data remains higher or equal to general population mortality rates maintaining clinical and demographic plausibility. Since general population mortality rates are relatively less affected by melanoma-related deaths compared to the trial population's mortality rates, capping OS extrapolations with general population mortality rates ensures that the survival projections remain clinically plausible.

Figure 17: Illustration of how the PFS and OS curves are used to estimate the health state occupancy in the PSM



Abbreviations: OS, Overall survival; PFS, Progression-free survival; PSM, Partitioned survival model.
Source: NICE DSU TSD19 (2017).[122]

3.2.2.3 Model conceptualization and justification of the approach

The PSM is a commonly used modelling approach in metastatic and relapsed/refractory oncological conditions. It is preferred to state-transition models (STM) in situations where mature PFS and OS data are available from the trials, such as the data from the C-144-01 trial, which provide robust extrapolation of both PFS and OS. Although the PSM and STM structures are similar as they are both based on PFS and OS, the STM approach requires splitting OS data into separate pre-progression and post-progression survival. This is necessary to calculate multiple transition probabilities between all health states included in the model. This results in lower number of events populating each transition, increasing uncertainty in the extrapolations. Since the C-144-01 trial provides patient-level data only for the lifileucel arm and the comparator data from the published literature are limited, deriving the multiple transition probabilities required for an STM approach for the comparator arm is not feasible and would require additional assumptions. Instead, the PSM approach, which uses proportions across the health states, is more suitable given the available

data. The PSM also allows for the key trial endpoint of the PFS and OS to be modelled directly, accurately reflecting the clinical pathway of the disease.

Furthermore, conducting an indirect treatment comparison of transition probabilities is a more complex approach compared to established methodologies for indirect comparisons of survival curve modelling. This further supports the use of PSM, as it provides a more straightforward approach of leveraging mature survival data for extrapolation. The PSM structure was also widely used and accepted in numerous NICE appraisals for metastatic melanoma, consistent with the findings from the SLR, where nine out of 12 appraisals identified used PSM, including NICE TA268, TA269, TA321, TA357, TA366, TA400, TA396, TA562 and TA950[68–71,73,75–77,115] Among the four published studies identified in the SLR, one utilised the PSM.[112] The PSM structure is simple, provides flexibility and allows for the direct use of time-to-event data from clinical trials, as detailed in the NICE Decision Support Unit (DSU) 19 guidance.[122] A review of previous NICE CAR-T appraisals in other disease areas also found that the PSM structure was predominantly used and accepted, such as NICE TA872 and TA893 and TA975.[118,119,121]

3.2.2.4 Time horizon and model cycle

A lifetime (45 years) time horizon was adopted to adequately capture the long-term treatment costs and the survival benefits, which is in line with the NICE reference case.[123] A weekly cycle length was used to allow sufficient granularity to accurately capture differences in cost and health effects between cycles, as well as account for the rapid progression of patients due to the severity of the disease. The model does not include half-cycle correction due to the short cycle length (in line with NICE TA357, TA321 and TA366).[69–71] A lifetime (45 years) time horizon was adopted to adequately capture the long-term treatment costs and the survival benefits, which is in line with the NICE reference case.[123] It is expected that a proportion of patients treated with lifileucel will be cured and exhibit survival rates approximating those of the general population. Additionally, a small proportion of patients on ipilimumab are expected to experience cure and consequently long-term survival. Based on these factors, a lifelong model horizon was applied with a maximum patient age of 100. With a starting age of [redacted] for patients entering the model, it resulted in a 45-year time horizon implemented in the model to capture the benefit of long-term survival for lifileucel and

comparators. The starting age of [redacted] was chosen as it was the mean age of the PDAwCS efficacy set in the C-144-01 trial.[86]

3.2.2.5 Perspective and discounting

In line with the NICE reference case, the analysis was conducted from the perspective of the National Health Service (NHS) and Personal Social Services (PSS) for both costs and health outcomes and a 3.5% discount rate per annum was applied to both costs and outcomes.[123]

In addition to the standard annual discounting, a scenario analysis was performed applying a reduced annual discount rate of 1.5% to both costs and clinical outcomes, as shown in Section 3.10.3. According to Section 4.5.3 of the NICE manual, the committee may consider using the non-reference discount rate of 1.5% in cases where specific criteria are met.[123]

The case for change consultation document for the NICE methods of health technology evaluation highlighted that "*NICE understands there is a significant policy-level drive to support curative and potentially curative technologies including advanced therapy medicinal products (ATMPs)" and "conclude that there is a case to reconsider the provisions for non-reference-case discounting".* The report defines *"ATMPs as gene therapies, cell therapies and tissue-engineered products, which have the potential to provide substantial health benefits, including potentially curative options for serious conditions*". The report further examined the use of the non-reference discount rate of 1.5% for technologies with high upfront costs and long-term health benefits, such as ATMPs and other one-off treatments.[124] Following the consultation, section 4.5.3 of the NICE manual reaffirmed that the committee may consider using the non-reference discount rate of 1.5% in cases where specific criteria are met.[123]

Lifileucel clearly satisfies these criteria as an ATMP, being a cell therapy and also a one-off treatment, with high upfront costs that provides long-term health benefits, including curative potential. This was further supported by The Association of the British Pharmaceutical Industry (ABPI) NICE Methods and Process Review Consultations which state that "*the current discount rate of 3.5% undervalues the longer-term benefits that medicines offer patients and their families and makes it difficult for innovations like cell and gene therapies to be recommended by NICE*".[125]

Table 29 outlines how lifileucel meets each requirement. This demonstrates that the reduced discount rate is appropriate for evaluating lifileucel's long-term cost-effectiveness and clinical benefits.

Table 29: Justification for applying a 1.5% discount rate based on NICE criteria[123]

NICE criteria	Justification
The technology is for people who would otherwise die or have a very severely impaired life.	In the UK, melanoma is responsible for 2,314 deaths a year.[126] Despite advances in first-line treatments for unresectable or metastatic melanoma, the prognosis remains poor, with most patients failing to achieve long-term benefits from available therapies. Survival outcomes after progression on first-line ICI therapy are poor, with real-world evidence showing a median OS ranging between 4.0 to 12.3 months in second-line or later treatment settings.[127,128] Furthermore, patients with unresectable, metastatic melanoma experience a lower (HRQoL) compared to patients living without cancer or with earlier stages of melanoma.[44] This is due to various factors affecting their physical well-being, emotional and psychological health and social well-being as discussed in detail in Section 3.4.
It is likely to restore them to full or near-full health.	In the C-144-01 trial (N=106, PDAwCS), the longest follow-up data for lifileucel (DCO 30th June 2023) had an evident plateau in the PFS and OS KM curves at approximately [redacted], with a median follow-up of 47 months.[86] This plateau indicates that a proportion of patients have achieved long-term survival, suggesting a curative effect for lifileucel. In the Pooled Cohorts 2 and 4 for the FAS population (N=153), the median DOR of lifileucel was [redacted] months after a median follow up of [redacted] months. The probability of remaining in response at 12 months was [redacted]%, at 24 months was [redacted] at 36 months was [redacted] and at 48 months was [redacted][86] The lifileucel PFS and OS extrapolations of the C-144-01 trial (PDAwCS) demonstrate cure rates of [redacted] and [redacted] (lifileucel unadjusted data) obtained from PFS and OS data respectively. If lifileucel data are adjusted for ipilimumab, the estimated PFS and OS rate at 5 years is [redacted] and [redacted] respectively (see Section 3.3.1.5). Among patients with both baseline and Week 12 data, the mean (SD) global health status/HRQoL scores were similar throughout all cohort analyses with baseline and Week 12 values of 69.2 (20.5) and 70.1 (21.2) respectively for pooled Cohorts 2 and 4.[86] While a decrease in QoL may occur directly after or during treatment with lifileucel, the consistent global health scores presented by the patient across the first three-month treatment period suggests that such a decrease would quickly subside and, as such,

	lifileucel effectively maintains patients' QoL during treatment. Among patients with both baseline and Month 6 data, the mean (SD) global health status/HRQoL scores were 73.4 (20.5) and 78.10 (18.3) respectively.[86] This indicates that patients that survive longer term have higher mean scores, reflecting an improvement in QoL for patients who benefit from treatment. (see section 2.6.4). All the evidence provided above supports lifileucel's curative effect and ability to restore full health in a significant proportion of patients.
The benefits are likely to be sustained over a very long period.	In the C-144-01 trial, the median OS reported for pooled cohort 2 and 4 in the FAS population was 13.9 months with a 4-year OS rate of 21.9%. This indicates that almost a quarter of patients treated with lifileucel survived at least 4 years, highlighting the potential of lifileucel to extend survival significantly.[86]

Abbreviations: HRQoL, Health-related quality of life; ICI, Immune checkpoint inhibitor; PFS, Progression-free survival; OS, Overall survival; QoL, Quality of life; SD, Standard deviation.

3.2.2.6 Model settings

A summary of the key features of the economic analysis in comparison to previous NICE appraisals for previously treated patients with unresectable or metastatic melanoma and their justification is provided in Table 30, Table 31 and Table 32.

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Table 30: Features of prior economic analyses in melanoma compared to current analysis (1/2)

Parameter	Previous melanoma evaluations						Current appraisal	
	TA268	**TA319**	**TA357**	**TA366**	**TA384**	**TA400**	**Chosen values**	**Justification**
Population	Advanced (unresectable or metastatic) melanoma in people who have received prior therapy	Adults with previously untreated advanced (unresectable or metastatic) melanoma	Advanced (unresectable or metastatic) melanoma in adults only: after the disease has progressed with ipilimumab and, for BRAF V600 mutation positive disease, a BRAF or MEK inhibitor	Advanced (unresectable or metastatic) melanoma that has not been previously treated with ipilimumab, in adults.	Advanced (unresectable or metastatic) melanoma in adults.	Advanced (unresectable or metastatic) melanoma in adults.	[redacted]	Aligned to the PDAwCS population of the pivotal C-144-01 trial, final scope, the decision problem and the anticipated UK licensed indication.
Intervention	Ipilimumab	Ipilimumab	Pembrolizumab	Pembrolizumab	Nivolumab	Nivolumab with ipilimumab	Lifileucel	N/A
Model type	Four-state PSM: baseline disease, non-progressive disease, progressive	Semi-Markov PSM: This model defines health states by treatment lines, using disease progression as proxy for	Three-state PSM: Pre-progression, post-progression and death.	Three-state PSM: Pre-progression, post-progression and death	Three-state semi-Markov model: pre-progression, progression and death. The semi-Markov model was chosen	The company used 2 different modelling approaches: a semi-Markov model (modelling transition	Three-state PSM: progression free, progressed disease and death	This approach is generally consistent with previous NICE submissions and considered the most appropriate modelling framework given

Parameter	Previous melanoma evaluations						Current appraisal	
	TA268	**TA319**	**TA357**	**TA366**	**TA384**	**TA400**	**Chosen values**	**Justification**
	disease and death	transitions. The approach of using health states as pre- and post-progression was deemed unsuitable because multiple active treatment lines exist and QoL is not directly linked to progression status.			over PSM because the post-progression survival data are more mature than OS, making extrapolations more valid and robust. It models survival using time to progression, pro-progression survival and post-progression survival instead of PFS and OS.	between the health states) for immunotherapies and a PSM (modelling health state occupancy) for the BRAF inhibitors. The ERG stated that the justification provided was inadequate and the company's model was unnecessarily complex and suggested a simpler approach such as the PSM.		the data available.
Time horizon	Lifetime (30 years)	Lifetime (40 years)	Lifetime (30 years)	Lifetime (30 years)	Lifetime (40 years)	Lifetime (40 years)	Lifetime horizon (45 years). The time horizon is defined as	This approach is in line with the NICE reference case. It covers

Parameter	Previous melanoma evaluations						Current appraisal	
	TA268	**TA319**	**TA357**	**TA366**	**TA384**	**TA400**	**Chosen values**	**Justification**
							maximum age of 100 years minus the baseline age, with the mean age of [redacted] years at baseline.	the period over which all differences in the costs and outcomes between treatments being compared would be observed.
Perspective	NHS and PSS	NHS and PSS	NHS and PSS	NHS and PSS	NHS and PSS	NHS and PSS	NHS and PSS	NICE reference case

Abbreviations: BSC, Best supportive care; ICER, Incremental cost-effectiveness ratio; LYG, Life years gained; MEK, Mitogen-activated protein kinase; N/R, Not reported; NHS, National health service; OS, Overall survival; PFS, Progression-free survival; QALY, Quality-adjusted life year; PSS, Personal social services.

Table 31: Features of prior economic analyses in melanoma compared to current analysis (2/2)

Parameter	Previous melanoma evaluations						Current appraisal	
	TA321	**TA269**	**TA396**	**TA410**	**TA562**	**TA950**	**Chosen values**	**Justification**
Population	Unresectable or metastatic BRAF V600 mutation positive melanoma	Advanced (unresectable or metastatic) melanoma in people who have received prior therapy.	Unresectable or metastatic melanoma in adults with a BRAF V600 mutation	Unresectable, regionally or distantly metastatic (stage 3B, 3C or 4M1a) melanoma that has not spread to bone, brain, lung or other	Unresectable or metastatic BRAF V600 mutation-positive melanoma in adults	Advanced (unresectable or metastatic) melanoma in people 12 years and over, only if nivolumab-relatlimab is stopped after 2 years of	[redacted]	Aligned to the PDAwCS population of the pivotal C-144-01 trial, final scope, the decision problem and the anticipated UK licensed indication.

Parameter	Previous melanoma evaluations						Current appraisal	
	TA321	TA269	TA396	TA410	TA562	TA950	Chosen values	Justification
				internal organs, only if treatment with systemically administered immunotherapies is not considered the best option by a multidisciplinary team		treatment, or earlier if the cancer progresses		
Intervention	Dabrafenib	Vemurafenib	Trametinib with dabrafenib	Talimogene laherparepvec	Encorafenib with binimetinib	Nivolumab-relatlimab	Lifileucel	N/A
Model type	Three-state PSM: progression-free, post-progression and death	Three-state PSM: progression-free, post-progression and death	Three-state PSM: PFS, PPS and death	Three-state PSM: PFS, post-progression and death.	Three-state PSM: Pre-progression, post-progression and death	Three-state PSM: progression-free, post-progression and death	Three-state PSM: progression free, progressed disease and death	This approach is generally consistent with previous NICE submissions.
Time horizon	Lifetime (30 years)	Lifetime (30 years)	Lifetime (30 years)	Lifetime (30 years)	Lifetime (30 years)	Lifetime (40 years)	The time horizon is defined as maximum age of 100 years minus the baseline age, with the mean age of [redacted] years at baseline.	This approach is in line with the NICE reference case.

Parameter	Previous melanoma evaluations						Current appraisal	
	TA321	TA269	TA396	TA410	TA562	TA950	Chosen values	Justification
Perspective	NHS and PSS	NHS and PSS	NHS and PSS	NHS and PSS	NHS and PSS	NHS and PSS	NHS and PSS	NICE reference case

Abbreviations: BSC, Best supportive care; ICER, Incremental cost-effectiveness ratio; LYG, Life years gained; MEK, Mitogen-activated protein kinase; N/R, Not reported; NHS, National health service; PFS, Progression-free survival; QALY, Quality-adjusted life year; PSS, Personal social services.

Table 32: Features of the CAR-T economic analyses

Parameter	Previous CAR-T evaluations					Current appraisal	
	TA677[117]	TA872[118]	TA893[119]	TA895[120]	TA975[121]	Chosen values	Justification
Population	Relapsed or refractory mantle cell lymphoma in adults who have previously had a Bruton's tyrosine kinase (BTK) inhibitor.	Relapsed or refractory DLBCL or primary mediastinal large B-cell lymphoma in adults after 2 or more systemic therapies.	Relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over.	Adult patients with DLBCL and high-grade Bcell lymphoma (HGBL) that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy.	People 25 years and under for treating B-cell acute lymphoblastic leukaemia that is: relapsed after a transplant, or relapsed for a second or later time, or refractory.	- [redacted]	Aligned to the PDAwCS population of the pivotal C-144-01 trial, final scope, the decision problem and the anticipated UK licensed indication.
Intervention	Brexucabtagene autleucel	Axicabtagene ciloleucel	Autologous anti-CD19-transduced CD3+ cells	Axicabtagene ciloleucel	Tisagenlecleucel	Lifileucel	N/A
Model type	PSM	PSM	PSM	PSM	PSM	PSM	This approach is generally

							consistent with previous NICE submissions.
Time horizon	Lifetime horizon (50 years)	Lifetime horizon (44 years)	Lifetime horizon (57 years)	Lifetime horizon (50 years)	Lifetime horizon (88 years)	Lifetime horizon (45 years)	This approach is in line with the NICE reference case.
Perspective	NHS and PSS	NHS and PSS	NHS and PSS	NHS and PSS	NHS and PSS	NHS and PSS	This approach is in line with the NICE reference case.
Cure effect	Cure effect was modelled through MCM. Cured patients' (long-term survivors') mortality was captured by SMR-adjusted age- and gender-matched general population mortality. Non-cured patients risk of progression was defined by standard parametric survival modelling. PFS and OS were modelled.	Cure effect was modelled through MCM. Cured patients' mortality was assumed identical to general population mortality. Survival in non-cured patients was modelled using a standard parametric survival model. PFS and OS were modelled.	Cure effect was modelled through MCM, however not used in the base case as the data was too immature to produce robust results using MCMs. Cured patients' mortality was captured by SMR-adjusted general population mortality. Survival in non-cured patients was modelled using a standard parametric survival model. EFS/PFS and OS were modelled.	Cure effect was modelled through MCM. Cured patients' mortality was captured by SMR-adjusted age- and gender-matched general population mortality. Non-cured patients risk of progression was defined by standard parametric survival modelling. EFS and OS were modelled.	Cure effect was modelled through MCM. Non-cured patients' survival trend was modelled by parametric survival curves and cured patients mortality trend followed a SMR- adjusted general population mortality. Cure fractions for MCMs were estimated separately for EFS and OS.	Cure effect was modelled through MCM and cured patients follow the general population mortality. Non-cured patients follow standard parametric survival extrapolations, reflecting disease-specific mortality.	This approach is in line with NICE DSU TSD 14 and 21.

Abbreviations: BTK, Bruton's tyrosine kinase; DLBCL, Diffuse large B-cell lymphoma; DSU, Decision Support Unit; EFS; Event-free survival; FAS, Final Approved Specification; HGBL, High-grade B cell lymphoma; MCM, Mixture cure modelling; MEK, Mitogen-activated kinase; N/A, Not applicable; NHS, National Health Service; PD-1, Programmed death-1; PSS, Personal Social Services; PSM, Partitioned Survival Model; TA, Technology Assessment; TSD, Technical support document.

3.2.2.7 Cure assumptions

The model includes a cure assumption for patients treated with lifileucel, where a proportion of patients would be cured at cycle 0, immediately following administration of lifileucel dose. This is determined using the mixture cure model approach, in addition to standard parametric modelling for the extrapolation of survival data. Cure assumption at time 0 is a common assumption for tractability in mixture cure modelling. The cure assumption is supported by an observed plateau in the PFS and OS KM curves from the C-144-01 trial (DCO 30th June 2023) of the PDAwCS at approximately [redacted] and [redacted], respectively with a median follow-up of 47.4 months as seen in Figure 8 and Figure 9. [86] More detailed justification and methodology description is provided in Section 3.3.1.1. The trial data are sufficiently mature to support this assumption, with endorsement from UK clinicians who have also stated that patients who remained alive without disease progression at three years and beyond are assumed cured with long-term survival similar to the general population.[16]

No cure assumption was applied to the chemotherapy or BSC arms due to the poor prognosis associated with these treatments and the lack of sufficient duration of a survival data plateau. Additionally, both treatments are not expected to provide curative potential based on their mechanism of action. Thus, a standard parametric survival modelling approach was used to extrapolate chemotherapy and BSC survival data. More detailed justification and methodology description is provided in Section 3.3.1.1.

Similarly, a cure assumption was not applied for the ipilimumab arm, given the lack of evidence supporting long-term survival in this patient population who are being treated with ipilimumab after being previously treated with PD-1 inhibitors and due to short study follow-up (22.1 months in da Silva).[88] The KM curve of ipilimumab from the da Silva *et al*. (2021) study did not demonstrate the survival plateau as seen in the lifileucel KM curve, however the follow-up in this study is limited (median of 22.1 months).[88] Thus, a standard parametric survival modelling approach was used to extrapolate ipilimumab survival data. However, UK clinical experts suggested that a small proportion of patients on ipilimumab monotherapy after PD-1 inhibitors, estimated at 1-5%, may achieve long-term survival.[129]

In the CheckMate 067 study, investigating nivolumab, ipilimumab and their combination for previously untreated advanced melanoma, the 10-year follow-up data displayed a strong association between 3-year PFS rates and long-term survivorship rates. Specifically, the 10-year OS rate among patients who were treated with ipilimumab and progression-free by year 3 was 79%; whereas in the intention-to-treat population, the respective 10-year OS rate was 19%. Moreover, the 10-year melanoma-specific survival (MSS) rate among patients who were treated with ipilimumab and progression-free by year 3 was 88%; whereas in the intention-to-treat population, the respective 10-year MSS rate was 23%. Compared with the intention-to-treat population in this study, consistent lower fractions of all-cause and melanoma-related deaths across 10 years among patients who were progression-free by year 3 are strong indicators of an association between the progression status by year 3 and long-term survivorship rates for patients treated with ipilimumab in front line melanoma, underlining the predictive value of PFS for cure and long-term survival.[130]

The functionality to assume that a proportion of ipilimumab patients who are progression-free at a defined timepoint achieve long-term survival has been included in the model (see section 3.3.1.4).

3.2.2.8 Lifileucel patient flow

There are several steps involved in the treatment process of lifileucel as described in detail in Section 1.2, Figure 2. The treatment steps include: (i) tumour tissue procurement to remove T-cells for manufacturing of lifileucel; (ii) preparing patients to receive lifileucel through a regimen of LD chemotherapy given over [redacted]; and (iii) infusion of lifileucel, followed by post-infusion administration of IL-2.[86]

Based on the C-144-01 trial, the median number of hospitalisation days related to tumour tissue procurement was [redacted] days. The autologous tumour sample is used as the source of the TIL to manufacture the active drug product, lifileucel, a cryopreserved infusion product. This process takes approximately 22 days, plus up to 2 weeks for product availablity.[86]

Patients enter the model when they are eligible for tumour tissue procurement for the process of lifileucel manufacturing. In line with the trial data, not all patients who may have their tumour harvested receive lifileucel due to premature discontinuation.

Reasons for premature discontinuation included adverse events, progression of disease or patient death. As a result, only a proportion of patients successfully proceeded to infusion of lifileucel. Additionally, not all infused patients received lifileucel doses that met the required specification (7.5×10^9 to 72×10^9 viable cells, as stated in the SmPC).[1] For patients who died after tumour resection and before getting the infusion, no further costs were assumed. For patients who discontinued treatment before lifileucel infusion, two approaches were considered for clinical outcomes and costs: either all patients move to BSC or they are distributed among available treatments based on their market shares. This is described in further detail in Section B.3.3.2.

3.2.2.9 Subsequent therapies

Subsequent therapies and treatment waning were not considered in the model due to patients' poor prognosis and lack of treatment options. Given that metastatic melanoma has a poor prognosis where patient's life expectancy will likely be less than one year after disease progression, patients will be unlikely to receive any active subsequent treatment and any treatment would likely be palliative in nature.[84,87,90,131,132] In addition, UK clinical experts have also noted that there are limited treatment options for patients receiving prior PD-1 inhibitor therapy regardless of their BRAF status, and after disease progression on a BRAF inhibitors with or without MEK inhibitors for BRAF-mutation positive patients .[16]

3.2.3 Intervention technology and comparators

The intervention of this appraisal is lifileucel and the comparators are ipilimumab, chemotherapy and BSC. The comparators are in line with the decision problem as described in Section 1.1 and validated with clinical experts following an advisory board meeting.[16]

3.2.3.1 Intervention: Lifileucel

Lifileucel is an autologous T cell immunotherapy, composing primarily of tumour-derived T cells of CD4+ and CD8+ T cell lineage. As described in Section 1.2, these tumour-derived T-cells work by entering tumour microenvironment, becoming TIL, and mediate tumour cell death.[133]

As described in Section 3.2.2.9, prior to lifileucel infusion, patients undergo surgical resection of tumour tissues, which are processed to manufacture TIL cell therapy. Patients are then pre-treated with an LD regimen consisting of:

- Cyclophosphamide: 60mg/kg IV with mesna (mesna is dosed as 60% of the cyclophosphamide dose) daily for 2 days[16,86,134]
- Fludarabine: 25mg/m^2 IV daily for 5 days[1,2]

Following the LD regimen, lifileucel is administered as a single dose infusion (one-off therapy) containing a suspension of the tumour-derived T cells, with a median dose in the C-144-01 trial of 20.87 x 10^9 viable cells.[86,133] Lifileucel is administered as soon as possible after 24 hours have elapsed from the last dose of LD chemotherapy, but no later than 4 days.[133]

IL-2 is then administered 3 to 24 hours post-lifileucel infusion at a dose of 600,000 IU/kg every 8 to 12 hours, up to a maximum of 6 doses, to promote cell expansion *in vivo.*[133]

3.2.3.2 Comparators: Ipilimumab

Based on the NICE NG14 guideline and NICE TA268, ipilimumab is recommended as an option for treating advanced (unresectable or metastatic) melanoma in people who have received prior therapy.[10,77] Since patients may be treated with pembrolizumab monotherapy, nivolumab monotherapy, or nivolumab plus relatlimab, combination therapy and were not yet treated with ipilimumab in the first-line setting, these patients may still be treated with ipilimumab monotherapy in the second-line plus setting. In TA950, clinical experts estimate that 20% of patients who have pembrolizumab or nivolumab monotherapy as a first line treatment are expected to be prescribed with ipilimumab monotherapy.[115] The recommended dose of ipilimumab, based on the NICE TA268 and the Summary of Product Characteristics (SmPC) is 3mg/kg administered intravenously over a 30-minute period every 3 weeks for a maximum of 4 doses.[77,135] Based on the expert opinion not all patients are expected to receive the full four maximum doses due to disease progression or toxicity concerns, the model incorporated a mean dose of 3.6 as the base case, with a an estimated duration of treatment at approximately 2.30 months. This approach was implemented by

weighting the number of doses based on the MDX-010 study by Hodi *et al*. (2010), which found that 64.2% of ipilimumab-alone group patients received all four ipilimumab doses.[33] UK clinical experts validated this methodology.[16] The da Silva *et al.* (2021) paper, the primary source for ipilimumab clinical efficacy data, was not used to estimate the mean dose as it only reported the maximum number of doses.[131] Additionally, a scenario analysis incorporating the administration of all four doses is also presented, as detailed in Section 3.10.3.

3.2.3.3 Comparators: Chemotherapy

Chemotherapy is recommended by NICE Melanoma guidelines for patients for whom ipilimumab, pembrolizumab, nivolumab, and targeted therapies are contraindicated.[10] The chemotherapy comparator in the model comprises of a basket of chemotherapy treatments. UK clinical experts confirmed the use of a basket of treatments given there is little to distinguish between the efficacy of different chemotherapy treatments on previously treated melanoma patients and the heterogeneity across treatments used for metastatic melanoma. They also validated that the basket of chemotherapy regimens was reflective of the standard of care patients in UK clinical practice.[16] The chemotherapy regimens included in the model are dacarbazine only, temozolomide only, carboplatin only, carboplatin + paclitaxel and dacarbazine + cisplatin. Additionally, only very limited data regarding clinical efficacy of each individual chemotherapy treatment were identified in the SLR making the indirect treatment comparisons and subsequent analyses infeasible on an individual treatment basis. Therefore, the same efficacy level was assumed for all chemotherapies above and it was modelled as a basket.

Dosing details of each chemotherapy treatment can be found in Table 33. Despite being clinically validated, most of the treatments did not have melanoma-specific posology described in the SmPC or the British National Formulary (BNF). Therefore, melanoma-related sources were used instead to determine the correct dosing. Whilst the frequency of administration for each chemotherapy was identified, there was a lack of relevant sources identifying the total duration for each chemotherapy. Therefore, it was assumed that all chemotherapies have a median time duration of 1.49 months based on Mangin *et al*. (2021), further validated by UK KOLs.[84] The weighting of each chemotherapy was informed by UK clinical experts and is presented in Table 34.[16]

Table 33: Summary of chemotherapy regimens

Treatment	Dosage regimen*	Administration method	Source
Dacarbazine only	850mg/m^2 on day 1 and then once every 3 weeks	IV	Dacarbazine SmPC[136] Klee *et al*.(2022)[137]
Temozolomide only	200 mg/m^2 orally for 5 days every 4 weeks	Oral	Quirbt *et al*. (2007)[138]
Carboplatin only	AUC 5 every 3 weeks	IV	Casper *et al*. (1990)[139], Dosing regimen was chosen based on clinical expert opinion[129]
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	IV	Flaherty *et al*. (2012)[140], Dosing regimen was chosen based on clinical expert opinion[129]
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	IV	Murren *et al*.(1991)[141], Dosing regimen was chosen based on clinical expert opinion[129]

Abbreviations: AUC, Area under the curve; IV, Intravenous; m, Metre; mg, Milligram; SmPC, Summary of Product Characteristics.
*Median time duration of 1.49 months from Mangin *et al.* (2021) was assumed for all chemotherapy regimen[84]

Table 34: Summary of chemotherapy weightings

Treatment	Weighting	Source
Dacarbazine only	65.00%	Clinical expert opinion[16]
Temozolomide only	10.00%	Clinical expert opinion[16]
Carboplatin only	5.00%	Clinical expert opinion[129]
Carboplatin + Paclitaxel	10.00%	Clinical expert opinion[129]
Dacarbazine + Cisplatin	10.00%	Clinical expert opinion[16]

Source: Lifileucel Advisory Board Report 2024 and 2025[16,129].

The chemotherapy clinical efficacy data in the economic model were based on Mangin *et al.* (2021). However, since the study is based on French clinical practice, its treatment regimens and weightings were not used. Instead, these were determined based on UK clinical expert opinion to better reflect UK clinical practice.

3.2.3.4 Comparators: BSC

Best supportive care is recommended by NICE Melanoma guidelines for patients for whom ipilimumab, pembrolizumab, nivolumab, and targeted therapies are contraindicated.[10] As described in Section 1.3.8, BSC implies that the patient does not receive systemic anti-cancer treatment. Instead, BSC consists of palliative care, radiotherapy, and emotional and practical support. UK clinicians agreed that BSC involves symptom and disease management.[16]

3.3 Clinical parameters and variables

This section describes the following:

1. The methodology, data inputs and results of the survival analyses approaches used to estimate and extrapolate PFS and OS over the lifetime horizon.

2. The discontinuation experienced in the C-144-01 trial between tumour harvest and receiving lifileucel infusion.

3. The adverse events (AEs) experienced in all the treatment arms.

3.3.1 Survival analysis

3.3.1.1 Survival analysis methodology

There were two key aspects considered for the survival analysis:

1. Unadjusted and adjusted survival analyses were employed:

   - Unadjusted survival analysis based on data from clinical trials: C-144-01 was a single arm trial therefore, no head-to-head clinical evidence exists for lifileucel and comparators. Hence, a naïve/unadjusted comparison of survival data was conducted. In this approach survival data for each intervention were taken from the respective clinical trials and were extrapolated separately.

   - Adjusted survival analysis based on STC: For lifileucel versus ipilimumab an STC were conducted. The hazard ratios (HRs) derived from the STC

were used in the model to adjust survival data (PFS and OS) of lifileucel to ipilimumab.

2. Standard parametric modelling (SPM) approach and a mixture cure modelling (MCM) approaches were used to extrapolate the survival data:

   - SPM was used for all interventions.

   - MCM approach was specifically used to extrapolate lifileucel survival data due to strength of its PFS and OS data, and its curative potential.

Adjusted and unadjusted survival analyses

The primary source for clinical efficacy of lifileucel, the C-144-01 trial, was a single-arm trial where Pooled Cohorts 2 and 4 data (PDAwCS) were used to assess lifileucel efficacy. To compare clinical efficacy (OS and PFS) between lifileucel and the comparators, two approaches were considered: unadjusted survival analysis based on data from clinical trials (for all comparators) and adjusted survival analysis based on STC outcomes (for ipilimumab only).

Unadjusted survival analysis *(all comparators)*

In the unadjusted survival analysis, data were analysed independently for each treatment and survival distributions were fitted to the corresponding KM data separately for each endpoint. These long-term distributions were incorporated into the model for both PFS and OS. This unadjusted method did not account for potential differences in study populations or biases.

Adjusted survival analysis based on STC *(lifileucel versus ipilimumab only)*

As discussed in Section 2.10, the adjusted ITC (STC) was only feasible for lifileucel versus ipilimumab due to patient characteristics between da Silva *et al*. (2021)[88] being similar enough to those in the C-144-01 trial; characteristics in the chemotherapy study (and therefore for BSC) was not similar enough to perform this analysis. As such, an STC between lifileucel and ipilimumab was performed to adjust for any imbalances in study populations and estimate an unbiased relative treatment effect (justification and methodology of STC is described in Section 2.10). As the company did not have

access to ipilimumab IPD, the lifileucel IPD were matched to the ipilimumab data and a hazard ratio for a lifileucel adjusted survival compared to ipilimumab survival was calculated as a result of STC.[142]

Additionally, hazard ratios were available from the unadjusted analysis for lifileucel versus ipilimumab (Section 2.10).

Based on these, to obtain the PFS and OS ratios for adjusted lifileucel versus unadjusted lifileucel, the company used the following equation:

$$\frac{Adjusted\ lifileucel\ vs\ ipilimumab\ HR\ (STC)}{Unadjusted\ lifileucel\ vs\ ipilimumab\ HR} = Adjusted\ vs\ Unadjusted\ lifileucel\ Ratio$$

For the PFS, the HR from STC for adjusted lifileucel versus ipilimumab was [redacted] and the PFS HR from unadjusted analysis for lifileucel versus ipilimumab was [redacted]. The resulting ratio for adjusted lifileucel versus unadjusted lifileucel was [redacted]. For the OS, HR from STC for adjusted lifileucel versus ipilimumab was [redacted] and the OS HR from unadjusted analysis for lifileucel versus ipilimumab was [redacted]. The resulting OS ratio for adjusted lifileucel versus unadjusted lifileucel was [redacted] These new ratios were applied to the unadjusted lifileucel survival curves to generate lifileucel curves adjusted for ipilimumab.

A simpler approach was considered where HRs for adjusted lifileucel versus ipilimumab from the STC were directly applied to the ipilimumab curves. However, the shape and tail of the lifileucel curve would no longer be maintained. This was deemed less plausible and not representative of lifileucel long-term survival.

Mixture cure modelling and standard parametric modelling

As described in Section 3.2.2.2, the proportion of patients alive in PF and PD health states of a PSM was determined by the extrapolation of PFS and OS data. An extrapolation of this data was required to determine the long-term survival as the follow-up periods for the relevant studies used in the analysis (median follow-up of 47.4 months for lifileucel in C-144-01[86]; 22.1 months for ipilimumab in da Silva *et al*. [2021][88]; and 12 months for both chemotherapy and BSC [given chemotherapy was

used as a proxy] in Mangin *et al.* [2021][84]) were shorter than the lifetime horizon used in the model (see Section 3.3.1.2 for more details on the efficacy data sources) .

Two modelling approaches were used for the extrapolation of survival data (both PFS and OS) from clinical trials:

1. Standard parametric modelling (SPM) – based on NICE DSU TSD 14 guidance using the package 'flexsurv' in R for all interventions in the analysis.[143,144]

2. Mixture cure modelling (MCM) – based on NICE DSU TSD 21 guidance using the package 'cuRE' in R for lifileucel only.[145,146]

Standard parametric modelling approach concept

In line with the NICE DSU TSD 14 guidance on survival analyses, a range of standard parametric distributions (exponential, Weibull, log-logistic, lognormal, Gompertz, and generalised gamma) were explored for survival data extrapolation. [143,144] The goodness-of-fit criteria (including the Akaike information criterion [AIC] and the Bayesian information criteria [BIC]) together with visual inspection and clinical validation were then used to select best fitting curve.

Mixture cure modelling approach concept

NICE DSU TSD 14 and 21 detailed the benefits towards using more flexible approaches for modelling survival when SPMs ability to capture more complex hazard functions is limited.[143,145] This was the case for extrapolating lifileucel survival data, as extrapolation of survival from the SPM did not adequately capture the observed plateau in lifileucel survival. MCM was an alternative approach that aimed to model PFS and OS to be more reflective of underlying clinical process and provide a more nuanced understanding of treatment effects.

MCM can be applied in situations where there is evidence supporting a proportion of the population being treated with a treatment as cured (see CAR-T TAs, as summarised in

Table 32). In the MCM, the population is divided into two distinct groups: those that are 'cured' of the disease and those that remain 'uncured'. The curative potential can

be interpreted as a potential of the therapy to minimize the risk of disease progression and disease related deaths for the disease population, but only for a 'cured' fraction of the disease population at a population level, not at the individual level. The proportion of patients considered 'cured' (i.e. the 'cure fraction') is assumed to be free of disease-related mortality and will experience long-term survival similar to the general population mortality (adjusted by a standardised mortality ratio [SMR]) from receiving a treatment throughout the lifetime horizon.

The cure rates for PFS were aligned with the strict definition of 'clinical cure', where the complete eradication of tumour cells is achieved. Therefore, once a patient progresses, they can no longer achieve long-term survival and cannot be considered cured. Cured patients are only at risk of non-disease-related deaths, with no risk of progression or disease-related mortality. Alternatively, the cure rates for OS represent the possibility of patients achieving long-term survival after progression and therefore it is a less conservative assumption. From this perspective, cured patients remain at risk of non-melanoma-related deaths. These distinctions should be considered when evaluating the of cure rates derived from MCM.

The remaining 'uncured' patients will continue to experience disease-related mortality and all-cause mortality, which is modelled using SPM approach.[145,147]

Both 'cured' patients with the SMR-adjusted general population mortality and 'uncured' patients with the survival analysis are then merged to provide the pooled survival estimates for the total population.

MCM approach was separately applied to PFS and OS data in the cost-effectiveness model.

Standard parametric modelling approach justification

The PFS KM curve for ipilimumab (Figure 12) showed a small plateau at approximately 15 months but lasted until approximately 19 months before decreasing thereafter. Similarly, a small plateau in the PFS KM curve for chemotherapy (Figure 14) was seen from approximately nine months until end of follow-up. However, this plateau was short (approximately three months) and misleading as the mechanism of action for chemotherapy is a hindrance to cure. Additionally, the OS curve for chemotherapy

exhibited a lack of plateau. This alongside the immature data represented by the follow-up time of 22.1 months and 12 months for ipilimumab and chemotherapy respectively, indicated that SPM was the most appropriate approach for modelling the survival of ipilimumab and chemotherapy (and therefore BSC). The modelling approaches for treatments were validated by five UK clinical experts at an advisory board (17th October 2024).[16] However, it was suggested by the clinical experts that some ipilimumab patients experience long-term survival. This was accounted for and detailed in Section 3.3.1.1.

Mixture cure modelling approach justification

The use of MCM was concluded to be appropriate for lifileucel as it reflected its curative potential. This was evident from the plateau observed in the PFS and OS KM curves from the C-144-01 trial (DCO 30th June 2023), presented in Section 2.10. The plateau in the PFS KM curve was observed between approximately [redacted] until end of follow-up [redacted][86] The plateau in the OS KM curve was observed between approximately [redacted] until end of follow-up [redacted]. This long-lasting plateau indicated that a proportion of patients have achieved long-term survival, suggesting a curative effect for lifileucel. This observation was in line with the proposed mechanism of action of lifileucel whereby the use of patient-specific T-cells creates a durable response potentially over a patient's lifetime. Additionally, the survival data found C-144-01 trial reached a total 4-year follow-up (median follow-up of 47.4) which signified data maturity.[133]

This modelling approach for lifileucel was validated by five UK clinical experts at an advisory board (17th October 2024), who stated that patients who remained alive without disease progression at three years and beyond were assumed cured with long-term survival similar to the general population, i.e. they expect a proportion of patients treated with lifileucel to obtain a similar mortality akin to general population mortality.[16]

This assumption is aligned with approaches used in CAR-Ts TAs, where a curative effect of CAR-Ts was demonstrated and extrapolated using the MCM approach, as summarized in Table 32, SPM was also used for extrapolation of lifileucel survival data (adjusted and unadjusted), distributions obtained from this approach did not

adequately capture the observed plateau in survival and thus SPM was not used in analysis for lifileucel.

Clinical plausibility

To ensure clinical plausibility of survival distributions, OS distributions were capped by standardised mortality ratio (SMR)-adjusted age- and gender-specific natural mortality of the general population to prevent overestimation of survival. This was calculated using the UK national life tables.[148] Further details on the SMR can be found in Section 3.3.1.3. Subsequently, survival distributions for PFS were capped by OS to avoid the logical inconsistency of the proportion of progression free patients being greater than patients alive. Survival distributions for all treatments were capped, regardless of whether the MCM or SPM approach was used.

3.3.1.2 Efficacy data sources

The primary efficacy outcomes considered in the analysis were PFS and OS, which informed the health state occupancy within the model (described further in Section 3.2.2.6).

Explicit modelling of time-to-treatment discontinuation (TTD) was not considered in the model through the survival analysis due to relatively short treatment durations of chemotherapy and ipilimumab, and the maximum four dose cap of ipilimumab. The estimated average duration of ipilimumab and chemotherapy were approximately 2.30 months and 1.49 months, respectively as described in Section 3.2.3.3 and 3.2.3.4. Lifileucel is a one-time infusion however, premature discontinuation of the cell therapy regimen (due to adverse events, progressive disease or the start of a new anti-cancer therapy) was included for lifileucel and is described further in Section 3.3.3.

Lifileucel efficacy source

PFS and OS data were obtained directly from the C-144-01 study (DCO 30th June 2023).[86] Lifileucel efficacy was estimated based on the PDAwCS (described further in Section 2.6). This analysis set represents patients who received lifileucel that met proposed SmPC dosing range (between ≥7.5 x 10^9 to ≤72 x 10^9 viable cells), the anticipated licensed dose in the UK, and manufactured at facilities approved for

commercial manufacturing. Data from Cohorts 2 and 4 were pooled and utilised as the base case of the model to maximise the sample size.

Ipilimumab efficacy source

As described in Section 2.1, five ipilimumab studies were identified in the SLR and supporting TLR that met the initial selection criteria for being used in the ITC. Only one study (da Silva *et al*. [2021][88]) was deemed relevant for the ITC. The use of the da Silva *et al*. (2021)[88] was validated by five UK clinical experts at an advisory board (17th October 2024).[16]

Chemotherapy efficacy source

As described in Section 2.1, two chemotherapy studies were identified in the SLR and supporting TLR that met the initial selection criteria used in the ITC. Only one study (Mangin *et al.* [2021][84]) was deemed relevant for the ITC. The use of Mangin *et al.* (2021)[84] was validated by five UK clinical experts at an advisory board (17th October 2024).[16]

BSC efficacy source

As described in Section 2.1, with recent transformation of metastatic melanoma treatment with immunotherapy and targeted therapies, no suitable and up-to-date data sources were identified for BSC within the published literature. Consequently, to model the efficacy of BSC, efficacy data from chemotherapy patients (Mangin *et al.* [2021][84]) was used as a proxy. Based on the advisory board (17th October 2024[16]), the five UK clinical experts agreed that BSC survival outcomes are approximately 50% worse than the chemotherapy. Therefore, a HR of two was applied to chemotherapy PFS and OS distributions and used as a proxy for BSC PFS and OS distributions, respectively.

3.3.1.3 Standardised mortality ratio

In the previous CAR-T appraisals (TA893[119], TA872[118] and TA677[117]), cancer patients who achieve long-term survival were associated with an increased risk of death compared to the age-equivalent general population. This is caused by co-morbidities obtained from the disease or the impact of receiving intensive treatments. The associated risk of death in melanoma patients who achieved long-term survival,

compared to that of general population survival, was assessed in this appraisal. To account for possible excess mortality, the SMR was applied, as a HR, to the background mortality rates and applied for cured lifileucel patients and patients that achieved long-term survival on ipilimumab (further details for ipilimumab long-term survival in Section 3.3.1.4). Background mortality rates were derived from the UK lifetables. [147]

Sadeq *et al*. (2023)[149] was a retrospective observational study on the US population used the Surveillance, Epidemiology, and End Results (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.

In addition, a retrospective analysis by Seitter *et al*. (2021)[150] 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. Similarly, Wolchok *et al*. (2024)[130], 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. These studies suggested that long-term survivors who remained PF at 3-5 years after melanoma treatment were no longer subject to melanoma-specific mortality.

To ensure that the SMR used in the model was reflective of UK patients and the patient population of interest, UK clinicians' opinion was sought through an advisory board (17th October 2024) and in 1:1 meetings.[16,129] UK clinicians stated that long term survivors of metastatic melanoma in our population of interest would be similar to a typical healthy person, emphasising a value of 1 for the SMR. Based on this, an SMR of 1 was used in the base case.

Moke et al. (2021)[151], utilising the SEER database, reported an SMR of 1.57 for melanoma survivors adolescents up to the age of 25 years. In this paper, a relatively younger population of adults compared to the patients in the C-144-01 trial was

assessed. Therefore, SMR of 1.57 was used in a scenario analysis where a HR of 1.57 was applied to the background mortality rates derived from the UK lifetables.

3.3.1.4 Long-term survival in ipilimumab patients

At the advisory board (17th October 2024), clinical experts indicated that a small proportion of patients treated with ipilimumab may achieve long-term survival.[16] This was optimistically estimated in the range of 1-5% of patients. This was dependent on the distribution of prior lines of treatments, which can influence the response to current treatment and therefore patients' likelihood of achieving long-term survival.

The identified literature for use of ipilimumab as a further line of treatment in melanoma suggested that the proportion of ipilimumab patients with a long-term survival was close to 0%. Using da Silva *et al*. (2021)[88] as a main efficacy source was validated at the advisory board. The short duration of a plateau and follow-up was insufficient to consider MCM (as described in Section 3.3.1.1) and therefore long-term survival for ipilimumab. Patrinely *et al*. (2020)[132], 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)[152] 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)[90] reported that ipilimumab administered after PD-1 therapy resulted in a 2-year survival rate of 3%. Wilson et al. (2021)[87], 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*".[87]

To account for clinical experts' feedback, the following approach was conducted to incorporate long-term survival of ipilimumab patients:

- It was assumed that percentage of patients that were PF at a defined time point (3-years in the base case, 5-years in the scenario analysis) achieved long-term survival.

- The OS of the PF patients from the defined time point onwards followed SMR-adjusted age- and gender-specific survival of the general population. The OS of the remaining patients who were not PF at the defined time point followed the modelled OS based on da Silva *et al*. (2021).[88]

3.3.1.5 Distribution selection for survival models

In accordance with NICE DSU TSD 14 and 21, a range of parametric distributions (exponential, Weibull, log-logistic, lognormal, Gompertz, and generalised gamma) were considered and fitted to the KM data.[145,147] For SPM, the distributions represent the extrapolated survival of the entire population. For MCM, the distributions represent the extrapolated survival of the uncured population. As for the cured population, SMR-adjusted general population mortality was assumed.

As mentioned in Section 3.3.1.1, OS was capped by SMR-adjusted age- and gender-specific natural mortality of the general population. In the base case, an SMR of 1 was utilised (Section 3.3.1). For a scenario analysis, Appendix O showed the modelled PFS and OS curves for an SMR of 1.57.

The following key criteria were considered for all treatment arms, regardless of survival analysis approach, when selecting the base-case distribution[143]:

- Statistical model fit, as measured by the AIC and BIC. The values were ranked with the lowest score in each indicating the distribution that had the best statistical fit.

- Log cumulative hazard plots to inspect the shape of the hazard function over time and assessing the suitability of dependent modelling between two treatments (plots were presented in 2.10).

- Visual inspection of survival curve fit to the KM data from the relevant clinical trials. The distribution that most closely resembled the KM curves are considered the best fit.

- UK clinician validation via the advisory board and 1:1 meetings.[16,129] This was considered to be the most important criteria when determining the distribution.

Full details of the distributions chosen and their justification for PFS and OS are provided in Section 3.3.1.5.

SPMs and MCMs to the unadjusted PFS data for lifileucel

For lifileucel, the PFS data were directly derived from IPD for C-144-01 (DCO 30th June 2023). The survival analysis was done on Pooled Cohorts 2 and 4 based on the PDAwCS. With a median follow-up of 47.4 months, the median PFS as assessed by the IRC was [redacted] for the Pooled Cohorts 2 and 4. No adjustments were made to the PFS data. The assessment of proportional hazards of lifileucel versus ipilimumab and chemotherapy (cumulative log-log plot, Schoenfeld residuals plot, quantile-quantile plot, hazard rate plots for PFS) are presented in Section 2.10.4 and Section 2.10.5, respectively.

The AIC and BIC statistical goodness-of-fit for the six distributions based on the unadjusted PFS data using the SPM approach was presented in Table 35. The extrapolations of PFS using each distribution up to 120 months were presented in Figure 18 to aid the investigation of the visual fit to the observed data and guide the assessment of long-term extrapolation clinical plausibility. The assessment of long-term extrapolation was further facilitated by the landmark survival estimates for each distribution, presented in Table 37.

Table 35: Goodness-of-fit statistics from SPMs to the unadjusted PFS data for lifileucel

Distribution	Lifileucel			
	AIC	AIC ranked	BIC	BIC ranked
Exponential	[redacted]	6	[redacted]	6
Weibull	[redacted]	5	[redacted]	5
Gompertz	[redacted]	2	[redacted]	2
Log-logistic	[redacted]	4	[redacted]	3
Log-normal	[redacted]	3	[redacted]	4
Generalised gamma	[redacted]	**1**	[redacted]	**1**

Abbreviations: AIC, Akaike Information Criteria; BIC, Bayesian Information Criteria; PFS, Progression-free survival; SPM, Standard parametric modelling.
Note: Results in bold are those that have the lowest AIC and BIC values.

Figure 18: KM curve for unadjusted PFS data overlaid with candidate SPM fits for lifileucel

Abbreviations: KM, Kaplan-Meier; PFS, Progression-free survival; SPM, Standard parametric modelling.

According to the AIC and BIC, the generalised gamma distribution provided the best statistical fit for unadjusted lifileucel PFS with the lowest individual AIC and BIC scores. The Gompertz distribution provided the second-best statistical fit however, given that it is >3 AIC points away, it was not comparable versus the generalised gamma distribution.[153] When investigating the visual fit, none of the distributions sufficiently captured the trend in unadjusted lifileucel PFS data. The 3-year PFS rates obtained from the fitted models were all lower than the observed 3-year PFS rate in the trial, highlighting the underestimation by the distributions.

The AIC and BIC statistical goodness-of-fit for six distributions based on unadjusted PFS data using the MCM approach along with the cure rates was presented in

Table 36. The extrapolations of PFS using each distribution up to 120 months were presented in Figure 19 and the landmark survival estimates for each distribution were presented in Table 37. The estimates and statistics presented reflect survival of pooled cured and uncured populations (with survival distributions for ‘uncured’ combined with general population survival adjusted by SMR for ‘cured’ patients).

Table 36: Goodness-of-fit statistics from MCMs to the unadjusted PFS data for lifileucel

Distribution	Lifileucel				
	Cure rate (95% CI)	AIC	AIC ranked	BIC	BIC ranked
Exponential	[redacted]	[redacted]	3	[redacted]	3
Weibull	[redacted]	[redacted]	4	[redacted]	4
Gompertz	[redacted]	[redacted]	5	[redacted]	5
Log-logistic	[redacted]	[redacted]	**1**	[redacted]	**1**
Log-normal	17.0% (10.0%, 25.5%)	[redacted]	2	[redacted]	2

Abbreviations: AIC, Akaike Information Criteria; BIC, Bayesian Information Criteria; CI, Confidence intervals; MCM, Mixture cure modelling; PFS, Progression-free survival.
Note: Results in bold are those that have the lowest AIC and BIC values. Convergence was not reached for generalised gamma MCM.

Figure 19: KM curve for unadjusted PFS data overlaid with candidate MCM fits for lifileucel

[redacted]

Abbreviations: KM, Kaplan-Meier; MCM, Mixture cure modelling; PFS, Progression-free survival.
Note: Convergence was not reached for generalised gamma MCM.

In contrast to SPM, each candidate MCM was reflective of the plateau as they effectively captured the change in the hazard function. This supported the use of MCM for lifileucel PFS in the base case analysis. The suitability of the MCM approach were further validated with UK clinicians.[16,129]

According to the AIC and BIC, the log-logistic MCM provided the best statistical fit for unadjusted lifileucel PFS with the lowest individual AIC and BIC scores. The log-normal MCM provided the second-best statistical fit and was comparable versus the log-logistic MCM (<3 AIC points away).[153] Both the visual fit and cure rates of log-logistic MCM ([redacted]) and log-normal MCM (17.0%) to the observed KM curve were similar. However, the exponential MCM also provided a similar visual fit and had a cure rate ([redacted]) that was more aligned to UK clinicians expectation ([redacted]).[16] To ascertain the most appropriate choice, UK clinicians' opinion was sought through 1:1 meetings.[129] Based on clinician feedback, log-normal MCM was used in the base case

of the model for unadjusted lifileucel PFS. Log-logistic MCM and exponential MCM were used in scenario analyses. A comparison of the observed and predicted PFS hazards for log-logistic MCM alongside general population OS hazards was presented in Figure 20. The observed hazards in the trial and predicted hazards from the selected MCM were aligned. Additionally, both the observed hazard from the trial data and the predicted hazards, reached the general population hazards, supporting usage of MCM.

Figure 20: Comparison of the observed and predicted PFS hazards for log-logistic MCM alongside general population OS hazards

Abbreviations: MCM, Mixture cure modelling; OS, Overall survival; PFS, Progression-free survival.
Note: General population OS hazards represent US lifetables.

Table 37: Landmark survival rates from SPMs and MCMs to the unadjusted PFS data for lifileucel

Survival analysis approach	Distribution	Mean (months)	Median (months)	Cure rate (95% CI)	PFS (%) at landmark timepoints							
					1/4-year	1/2-year	1-year	3-year	5-year	10-year	30-year	40-year
-	KM data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SPM	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MCM	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	17.0% (10.0%, 25.5%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, Confidence interval; KM, Kaplan-Meier; MCM, Mixture cure modelling; PFS, Progression-free survival; SPM, Standard parametric modelling.
Note: Convergence was not reached for generalised gamma MCM.

MCMs to the adjusted PFS data for lifileucel

As described in Section 3.3.1.1, lifileucel data were adjusted for ipilimumab to account for any imbalances between the study populations of the corresponding trials of two treatments. The ratio between the adjusted lifileucel versus unadjusted lifileucel ([redacted]) was calculated based on outcomes from STC and unadjusted analysis (versus ipilimumab) and was used to adjust lifileucel survival curves. Log-normal MCM was used as a base case for the adjusted approach to reflect the clinically validated choice for the unadjusted approach. The landmark survival estimates for the adjusted approach and the extrapolations up to 120 months are presented in Table 38 and Figure 21, respectively.

Table 38: Landmark survival rates from MCMs to the adjusted PFS data for lifileucel versus ipilimumab

Distribution	Mean (months)	Median (months)	PFS (%) at landmark timepoints							
			1/4-year	1/2-year	1-year	3-year	5-year	10-year	30-year	40-year
KM data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: KM, Kaplan-Meier; MCM, Mixture cure modelling; PFS, Progression-free survival.
Note: Convergence was not reached for generalised gamma MCM.

Figure 21: KM curve for adjusted PFS data overlaid with candidate MCM fits for lifileucel versus ipilimumab

[redacted]

Abbreviations: KM, Kaplan-Meier; MCM, Mixture cure modelling; PFS, Progression-free survival.
Note: Convergence was not reached for generalised gamma MCM. The difference between duration of the unadjusted lifileucel KM curve and adjusted lifileucel KM curve was due to how the company predicted when patients would still be at risk of an event (when there was at least one censored event).

SPMs to the PFS data for ipilimumab

For ipilimumab, the PFS data were obtained from da Silva *et al*. (2021).[88] As described in Section 2.9, in the absence of IPD for ipilimumab, survival data were reconstructed from the KM curves published in the trial using a validated two-step approach involving curve digitization and the Guyot algorithm.[108] This method is widely accepted for

survival curve reconstruction and was validated to provide reliable approximations when IPD is unavailable.

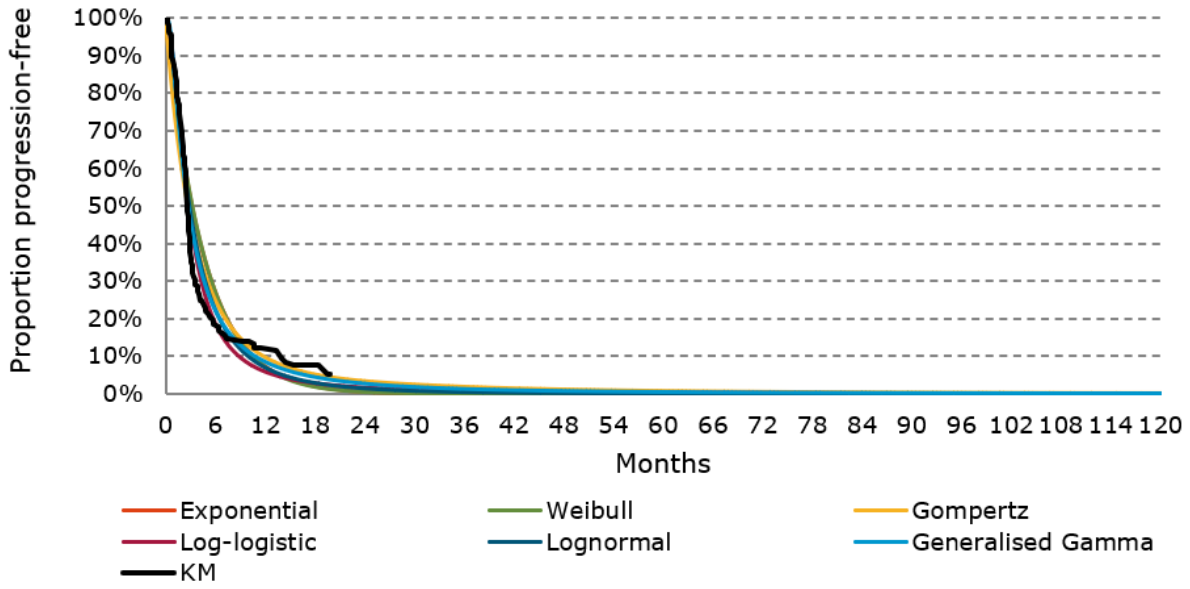
The AIC and BIC statistical goodness-of-fit metrics for the six distributions for ipilimumab PFS using the SPM approach is presented in Table 39. The extrapolations of PFS using each distribution up to 120 months are presented in Figure 22 to aid the investigation of the visual fit to the observed data and guide the assessment of long-term extrapolation clinical plausibility. The assessment of long-term extrapolation is further facilitated by the landmark survival estimates for each distribution, presented in Table 13.

Table 39: Goodness-of-fit statistics from SPMs to the PFS data for ipilimumab

Distribution	Ipilimumab			
	AIC	AIC rank	BIC	BIC rank
Exponential	734.21	5	737.29	6
Weibull	736.13	6	742.30	6
Gompertz	725.89	4	732.06	4
Log-logistic	**688.72**	**1**	**694.89**	**1**
Log-normal	695.36	3	701.53	2
Generalised gamma	692.75	2	702.01	3

Abbreviations: AIC, Akaike Information Criteria; BIC, Bayesian Information Criteria; PFS, Progression-free survival; SPM, Standard parametric modelling.
Note: Results in bold are those that have the lowest AIC and BIC values.

Figure 22: KM curve for PFS overlaid with candidate SPM fits for ipilimumab



Abbreviations: KM, Kaplan-Meier; PFS, Progression-free survival; SPM, Standard parametric modelling.

Table 40: Landmark survival rates from SPMs to the PFS data for ipilimumab

Distribution	Mean (months)	Median (months)	PFS (%) at landmark timepoints							
			1/4-year	1/2-year	1-year	3-year	5-year	10-year	30-year	40-year
KM data	-	2.6	38%	18%	12%	-	-	-	-	-
Exponential	4.7	3.0	52%	27%	7%	0%	0%	0%	0%	0%
Weibull	4.7	3.2	53%	27%	7%	0%	0%	0%	0%	0%
Gompertz	5.8	2.5	47%	25%	10%	2%	1%	0%	0%	0%
Log-logistic	4.7	2.5	46%	19%	6%	1%	0%	0%	0%	0%
Log-normal	4.7	2.8	48%	22%	7%	0%	0%	0%	0%	0%
Generalised gamma	5.3	2.5	46%	22%	9%	1%	0%	0%	0%	0%

Abbreviations: KM, Kaplan-Meier; PFS, Progression-free survival; SPM, Standard parametric modelling.

According to the AIC and BIC, the log-logistic distribution provided the best statistical fit for ipilimumab PFS with the lowest individual AIC and BIC scores. The second-best statistical fit was generalised gamma distribution according to AIC and log-normal distribution according to BIC. Both are not comparable versus the log-logistic distribution as they were >3 AIC points away from the log-logistic distribution.[153] The visual fit of the log-logistic distribution was the closest to the KM curve whilst both log-normal and generalised gamma distributions were similar to each other. To ascertain the most appropriate choice, UK clinicians' opinion was sought through 1:1

meetings.[129] Based on clinician feedback, log-logistic distribution was used in the base case of the model for ipilimumab PFS.

SPMs to the PFS data for chemotherapy

For chemotherapy, the PFS data was obtained from Mangin *et al*. (2021).[84] Similar to ipilimumab PFS, survival data were reconstructed from the KM curves published in the trial using a validated two-step approach involving curve digitization and the Guyot algorithm.[108]

The AIC and BIC statistical goodness-of-fit metrics for the six distributions for chemotherapy PFS using the SPM approach is presented in Table 41. The extrapolations of PFS using each distribution up to 120 months are presented in Figure 23to aid the investigation of the visual fit to the observed data and guide the assessment of long-term extrapolation clinical plausibility. The assessment of long-term extrapolation is further facilitated by the landmark survival estimates for each distribution, presented in

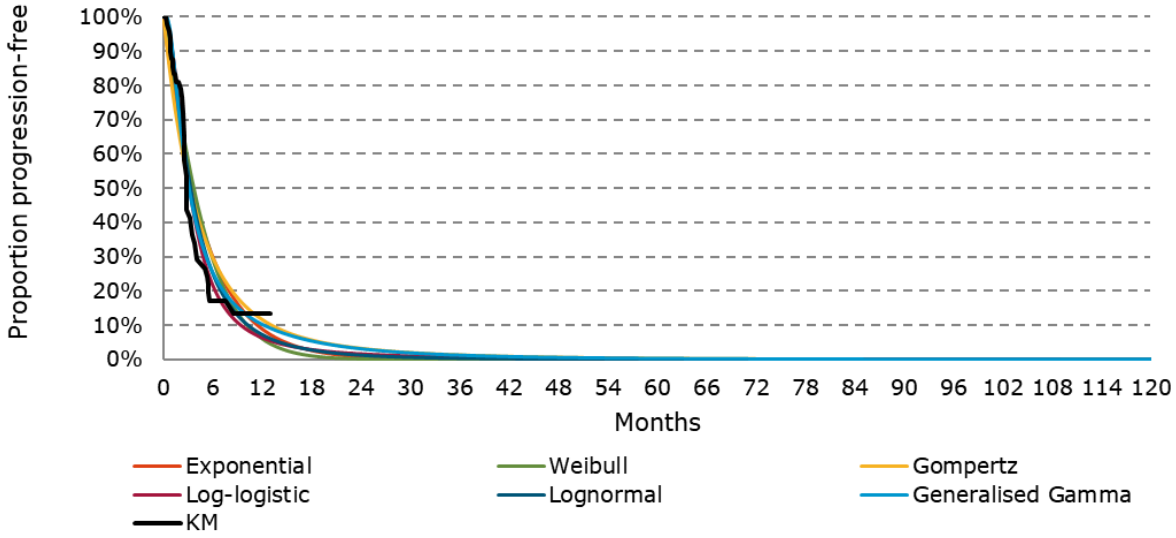
Table 42.

Table 41: Goodness-of-fit statistics from SPMs to the PFS data for chemotherapy

Distribution	Chemotherapy			
	AIC	AIC rank	BIC	BIC rank
Exponential	194.46	4	196.38	4
Weibull	194.77	5	198.60	5
Gompertz	195.83	6	199.65	6
Log-logistic	**182.86**	**1**	**186.69**	**1**
Log-normal	184.13	2	187.95	2
Generalised gamma	184.15	3	189.89	3

Abbreviations: AIC, Akaike Information Criteria; BIC, Bayesian Information Criteria; PFS, Progression-free survival; SPM, Standard parametric modelling.
Note: Results in bold are those that have the lowest AIC and BIC values.

Figure 23: KM for PFS overlaid with candidate SPM fits for chemotherapy



Abbreviations: KM, Kaplan-Meier; PFS, Progression-free survival; SPM, Standard parametric modelling.

Table 42: Landmark survival rates from SPMs to the PFS data for chemotherapy

Distribution	Mean (months)	Median (months)	PFS (%) at landmark timepoints							
			1/4-year	1/2-year	1-year	3-year	5-year	10-year	30-year	40-year
KM data	-	2.8	44%	17%	14%	-	-	-	-	-
Exponential	5.1	3.2	55%	30%	9%	0%	0%	0%	0%	0%
Weibull	4.8	3.4	58%	29%	6%	0%	0%	0%	0%	0%
Gompertz	5.9	3.0	52%	30%	12%	1%	0%	0%	0%	0%
Log-logistic	4.9	3.0	53%	22%	6%	1%	0%	0%	0%	0%
Log-normal	5.0	3.2	54%	25%	7%	0%	0%	0%	0%	0%
Generalised gamma	5.7	3.0	51%	25%	10%	1%	0%	0%	0%	0%

Abbreviations: KM, Kaplan-Meier; PFS, Progression-free survival; SPM, Standard parametric modelling.

According to the AIC and BIC, the log-logistic distribution provided the best statistical fit for chemotherapy PFS with the lowest individual AIC and BIC scores. The second-best statistical fit was log-normal distribution which, alongside generalised gamma distribution, were considered comparable fit to log-logistic distribution (<3 AIC away).[153] The visual fit of all three distributions were similar to each other. To ascertain the most appropriate choice, UK clinicians' opinion was sought through an advisory board (7th October 2024).[16] Based on clinician feedback, log-logistic distribution was used in the base case of the model for chemotherapy PFS.

SPMs to the PFS data for BSC

As mentioned in Section 3.3.1.1, Mangin *et al.* (2021)[84] was used as a proxy due to the lack of available data sources representing BSC. Based on the advisory board (17th October 2024[16]), a HR of two was applied to chemotherapy PFS to reflect the likely efficacy of patients receiving BSC. Log-logistic distribution was used for the base case, reflecting the clinician choice for the PFS of chemotherapy patients. The landmark survival estimates are presented in Table 43.

Table 43: Landmark survival rates from SPMs to the PFS data for BSC

Distribution	Mean (months)	Median (months)	PFS (%) at landmark timepoints							
			1/4-year	1/2-year	1-year	3-year	5-year	10-year	30-year	40-year
Exponential	2.3	1.6	26%	5%	0%	0%	0%	0%	0%	0%
Weibull	2.5	1.8	29%	5%	0%	0%	0%	0%	0%	0%
Gompertz	2.2	1.4	24%	4%	0%	0%	0%	0%	0%	0%
Log-logistic	2.6	1.8	28%	5%	0%	0%	0%	0%	0%	0%
Log-normal	2.6	1.8	30%	5%	0%	0%	0%	0%	0%	0%
Generalised gamma	2.5	1.8	26%	5%	0%	0%	0%	0%	0%	0%

Abbreviations: BSC, Best supportive care; KM, Kaplan-Meier; PFS, Progression-free survival; SPM, Standard parametric modelling.

SPMs and MCMs to the unadjusted OS data for lifileucel

Consistent with lifileucel PFS, the OS data were directly derived from IPD for C-144-01 (DCO 30th June 2023) with the survival analysis on Pooled Cohorts 2 and 4 based on the PDAwCS. With a median follow-up of 47.4 months, the median OS was [redacted] for the Pooled Cohorts 2 and 4. No adjustments were made to the OS data. The assessment of proportional hazards of lifileucel versus ipilimumab and chemotherapy (cumulative log-log plot, Schoenfeld residuals plot, quantile-quantile plot, hazard rate plots for OS) were presented in Sections 2.10.4 and 2.10.5, respectively.

The AIC and BIC statistical goodness-of-fit for these six distributions for unadjusted lifileucel OS using the SPM approach were presented in Table 44. The AIC and BIC are presented for each parametric distribution. The extrapolations of OS using each distribution up to 120 months are presented in Figure 24 to aid the investigation of the visual fit to the observed data and guide the assessment of long-term extrapolation with clinical plausibility. The assessment of long-term extrapolation is further

accompanied by the landmark survival estimates for each distribution, presented in Table 46.

Table 44: Goodness-of-fit statistics from SPMs to the unadjusted OS data for lifileucel

Distribution	Lifileucel			
	AIC	AIC ranked	BIC	BIC ranked
Exponential	[redacted]	6	[redacted]	6
Weibull	[redacted]	5	[redacted]	5
Gompertz	[redacted]	**1**	[redacted]	**1**
Log-logistic	[redacted]	3	[redacted]	3
Log-normal	[redacted]	2	[redacted]	2
Generalised gamma	[redacted]	4	[redacted]	4

Abbreviations: AIC, Akaike Information Criteria; BIC, Bayesian Information Criteria; OS – Overall survival; SPM, Standard parametric modelling.
Note: Results in bold are those that have the lowest AIC and BIC values.

Figure 24: KM curve for unadjusted OS overlaid with candidate SPM fits for lifileucel

[redacted]

Abbreviations: KM, Kaplan-Meier; OS, Overall survival; SPM, Standard parametric modelling.

According to the AIC and BIC, the Gompertz distribution provided the best statistical fit for unadjusted lifileucel OS with the lowest individual AIC and BIC scores. The log-normal distribution provided the second-best statistical fit which, alongside log-normal, log-logistic and generalised gamma distribution, were comparable versus the Gompertz distribution (<3 AIC points away).[153] The landmark survival rates at 3-years suggested that the distributions captured the trend in unadjusted lifileucel OS data as they were all similar to the 3-year PFS rate in the trial. However, when investigating the visual fit, none of the distributions for unadjusted lifileucel OS sufficiently captured the plateau in the KM curve.

The AIC and BIC statistical goodness-of-fit for these six distributions for unadjusted lifileucel OS using the MCM approach along with the cure rates are presented in Table 45. The extrapolations of PFS using each distribution up to 120 months are presented in Figure 25 and the landmark survival estimates for each distribution are presented in Table 46. The estimates and statistics presented reflect survival of both the cured and uncured populations (with survival distributions for 'uncured' combined with general population survival adjusted by SMR for 'cured' patients).

Table 45: Goodness-of-fit statistics from MCMs to the unadjusted OS data for lifileucel

Distribution	Lifileucel				
	Cure rate (95% CI)	AIC	AIC ranked	BIC	BIC ranked
Exponential	25.7% (16.7%, 35.7%)	[redacted]	**1**	[redacted]	**1**
Weibull	[redacted]	[redacted]	4	[redacted]	4
Gompertz	[redacted]	[redacted]	5	[redacted]	5
Log-logistic	[redacted]	[redacted]	2	[redacted]	2
Log-normal	[redacted]	[redacted]	3	[redacted]	3
Generalised gamma	[redacted]	[redacted]	6	[redacted]	6

Abbreviations: AIC, Akaike Information Criteria; BIC, Bayesian Information Criteria; MCM, Mixture cure modelling; OS, Overall survival.
Notes: Results in bold are those that have the lowest AIC and BIC values. Convergence was not reached in one of the parameters for Gompertz and generalised gamma MCM.

Figure 25: KM curve for unadjusted OS data overlaid with candidate MCM fits for lifileucel

[redacted]

Abbreviations: KM, Kaplan-Meier; MCM, Mixture cure modelling; OS, Overall survival.
Note: Convergence was not reached in one of the parameters for Gompertz and generalised gamma MCM.

Similar to lifileucel PFS, each candidate MCM was reflective of the plateau as they effectively captured the change in the hazard function. This supports the use of MCM for lifileucel OS in the base case analysis, is consistent with the approach used for lifileucel PFS and is validated by UK clinicians.[16,129]

According to the AIC and BIC, the exponential MCM provided the best statistical fit for unadjusted lifileucel OS with the lowest individual AIC and BIC scores. Log-logistic MCM was considered the second-best statistical fit however, it is important to note that all the other distributions are considered as comparable fits as they are within <3 AIC points away from the exponential MCM.[153] The visual fits to the KM curve from these MCMs were also similar. Exponential MCM was clinically intuitive as it assumed uncured patients die at a constant rate, implying that their survival curve does not flatten which was clinically expected for the uncured patients. To ascertain the most appropriate choice, UK clinicians' opinion was sought through 1:1 meetings.[129] Based

on clinician feedback, exponential MCM is used in the base case of the model for unadjusted lifileucel OS with log-logistic MCM being used in scenario analyses.

A comparison of the observed and predicted OS hazards for exponential MCM alongside general population OS hazards is presented in Figure 26. The observed hazards in the trial and predicted hazards from the selected MCM were aligned. Additionally, both the observed hazard from the trial data and the predicted hazards, reached the general population hazards, supporting usage of MCM.

Figure 26: Comparison of the observed and predicted OS hazards for exponential MCM alongside general population OS hazards

Abbreviations: MCM, Mixture cure modelling; OS, Overall survival.
Note: General population OS hazards represent US lifetables.

Table 46: Landmark survival rates from SPMs and MCMs to the unadjusted OS data for lifileucel

Survival analysis approach	Distribution	Mean (months)	Median (months)	Cure rate	OS (%) at landmark timepoints							
					1/4-year	1/2-year	1-year	3-year	5-year	10-year	30-year	40-year
-	KM data	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SPM	Exponential	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MCM	Exponential	[redacted]	[redacted]	25.7% (16.7%, 35.7%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: KM, Kaplan-Meier; MCM, Mixture cure modelling; OS, Overall survival; SPM, Standard parametric modelling.
* Convergence was not reached.

MCMs to the adjusted OS data for lifileucel

As described in in Section 3.3.1.1 for lifileucel PFS, lifileucel data were adjusted for ipilimumab to account for any imbalances between the study populations of the corresponding trials of two treatments. The ratio between the adjusted lifileucel versus unadjusted lifileucel ([redacted]) was calculated based on outcome from STC and unadjusted analysis (versus ipilimumab) and was used to adjust lifileucel survival curves. Exponential MCM was used for the adjusted approach to reflect the clinically validated choice for the unadjusted approach. The landmark survival estimates for the adjusted approach and the extrapolations up to 120 months are presented in Table 47 and Figure 27, respectively.

Table 47: Landmark survival rates from MCMs to the adjusted OS data for lifileucel versus ipilimumab

Distribution	Mean (months)	Median (months)	OS (%) at landmark timepoints							
			1/4-year	1/2-year	1-year	3-year	5-year	10-year	30-year	40-year
KM data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: KM, Kaplan-Meier; MCM, Mixture cure modelling; OS, Overall survival.

Figure 27: KM curve for adjusted OS data overlaid with candidate MCM fits for lifileucel versus ipilimumab

[redacted]

Abbreviations: KM, Kaplan-Meier; MCM, Mixture cure modelling; OS, Overall survival.
Note: The difference between the follow up unadjusted lifileucel KM curve and adjusted lifileucel KM curve was due to how the company predicted when patients would still be at risk of an event (when there was at least one censored event).

SPMs to the OS data for ipilimumab

Consistent with ipilimumab PFS, in the absence of IPD, the OS data were reconstructed from the KM curves published in da Silva et al. (2021).[88]

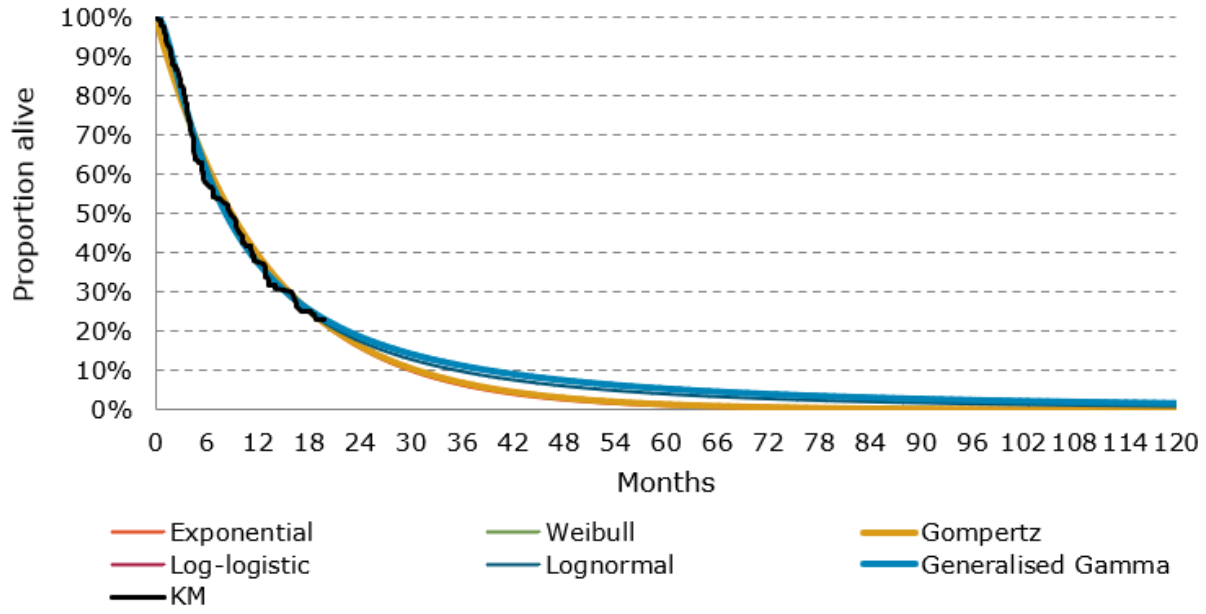
The AIC and BIC statistical goodness-of-fit criteria for the six distributions for ipilimumab OS using the SPM approach is presented in Table 48. The extrapolations of OS using each distribution up to 120 months are presented in Figure 28 to aid the investigation of the visual fit to the observed data and guide the assessment of long-term extrapolation clinical plausibility. The assessment of long-term extrapolation is further facilitated by the landmark survival estimates for each distribution, presented in Table 49. These estimates reflect the direct fit of the survival distributions to the KM data without the adjustment of long-term survival for ipilimumab patients (detailed in Section 3.3.1.4).

Table 48: Goodness-of-fit statistics from SPMs to the OS data for ipilimumab

Distribution	Ipilimumab			
	AIC	AIC ranked	BIC	BIC ranked
Exponential	750.66	5	753.75	4
Weibull	750.59	4	756.77	5
Gompertz	752.63	6	758.81	6
Log-logistic	742.24	3	748.41	2
Log-normal	**739.47**	**1**	**745.64**	**1**
Generalised gamma	741.12	2	750.39	3

Abbreviations: AIC, Akaike Information Criteria; BIC, Bayesian Information Criteria; MCM, Mixture cure modelling; OS, Overall survival.

Figure 28: KM curve for OS overlaid with extrapolations from SPMs for Ipilimumab



Abbreviations: KM, Kaplan-Meier; OS, Overall survival; SPM, Standard parametric modelling.

Table 49: Landmark survival rates from SPMs to the OS data for ipilimumab

Distribution	Mean (months)	Median (months) (months)	PFS (%) at landmark timepoints						
			1/4-year	1/2-year	1-year	3-year	5-year	30-year	40-year
KM data	-	8.7	84%	58%	38%	-	-	-	-
Exponential	13.1	9.0	79%	63%	40%	6%	1%	0%	0%
Weibull	12.4	9.2	82%	65%	40%	4%	0%	0%	0%
Gompertz	13.4	8.7	79%	63%	40%	7%	1%	0%	0%
Log-logistic	17.8	8.3	82%	62%	37%	10%	5%	2%	0%
Log-normal	15.9	8.3	82%	62%	38%	10%	4%	1%	0%
Generalised gamma	17.9	8.0	82%	61%	38%	11%	5%	2%	0%

Abbreviations: KM, Kaplan-Meier; OS, Overall survival; PFS, Progression-free survival; SPM, Standard parametric modelling.

According to the AIC and BIC, the log-normal distribution provided the best statistical fit for ipilimumab OS with the lowest individual AIC and BIC scores. The second-best statistical fits were generalised gamma distribution according to AIC and log-logistic distribution according to BIC. Both were comparable versus the log-logistic distribution (<3 AIC points away).[153] All distributions provided a similar visual fit to the KM curve. To ascertain the most appropriate choice, UK clinicians' opinion was sought through 1:1 meetings.[129] Based on clinician feedback, log-normal distribution was used in the base case of the model for ipilimumab OS and log-logistic distribution as a scenario analysis .

SPMs to the OS data for chemotherapy

Consistent with chemotherapy PFS, in the absence of IPD for chemotherapy, the OS data were reconstructed from the KM curves published in Mangin *et al.* (2021).[84]

The AIC and BIC statistical goodness-of-fit for the six distributions for chemotherapy OS using the SPM approach is presented in Table 50. The extrapolations of OS using each distribution up to 120 months are presented in Figure 29 to aid the investigation of the visual fit to the observed data and guide the assessment of long-term extrapolation clinical plausibility. The assessment of long-term extrapolation is further facilitated by the landmark survival estimates for each distribution, presented in

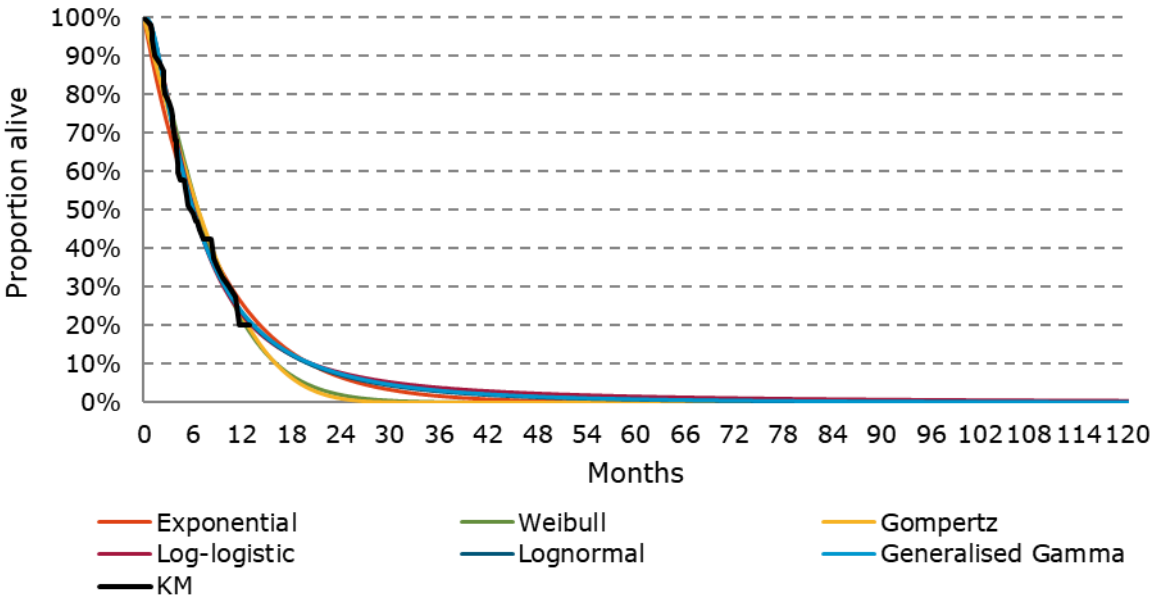
Table 51.

Table 50: Goodness-of-fit statistics from SPMs to the OS data for chemotherapy

Distribution	Chemotherapy			
	AIC	AIC ranked	BIC	BIC ranked
Exponential	237.22	5	239.14	4
Weibull	235.19	4	239.01	3
Gompertz	237.62	6	241.44	6
Log-logistic	233.56	2	237.39	2
Log-normal	**232.56**	**1**	**236.39**	**1**
Generalised gamma	234.56	3	240.29	5

Abbreviations: AIC, Akaike Information Criteria; BIC, Bayesian Information Criteria; MCM, Mixture cure modelling; OS, Overall survival.

Figure 29: KM curve for OS overlaid with candidate SPM fits for chemotherapy



Abbreviations: KM, Kaplan-Meier; OS, Overall survival; SPM, Standard parametric modelling.

Table 51: Landmark survival rates from SPMs to the OS data for chemotherapy

Distribution	Mean (months)	Median (months) (months)	OS (%) at landmark timepoints						
			1/4-year	1/2-year	1-year	3-year	5-year	30-year	40-year
KM data	-	5.4	80%	51%	20%	-	-	-	-
Exponential	9.0	6.0	71%	51%	26%	2%	0%	0%	0%
Weibull	8.1	6.4	79%	55%	22%	0%	0%	0%	0%
Gompertz	7.9	6.4	76%	54%	23%	0%	0%	0%	0%
Log-logistic	10.6	6.0	78%	51%	23%	4%	2%	0%	0%

Log-normal	9.5	6.0	77%	51%	23%	3%	1%	0%	0%
Generalised gamma	9.7	6.0	77%	50%	24%	3%	1%	0%	0%

Abbreviations: KM, Kaplan-Meier; OS, Overall survival; SPM, Standard parametric modelling.

According to the AIC and BIC, the log-normal distribution provided the best statistical fit for chemotherapy OS with the lowest individual AIC and BIC scores. The second-best statistical fit was the log-normal distribution which, alongside log-logistic, generalised gamma and Weibull distribution, were considered comparable fit to log-logistic distribution (<3 AIC points away).[153] All distributions provided a similar visual fit to the KM curve. To ascertain the most appropriate model choice, UK clinicians' opinion was sought through an advisory board (7th October 2024).[16] Based on clinician feedback, log-normal distribution was used in the base case of the model for chemotherapy OS.

SPMs to the OS data for BSC

Consistent with BSC PFS, Mangin *et al.* (2021)[84] was used as a benchmark to derive the OS curve for BSC patients. More specifically, a HR of two applied to best-fitting OS curve of chemotherapy patients to derive the OS trend of BSC patients.[16]. The log-normal distribution was used for the base case, reflecting the clinician choice for the OS of chemotherapy patients. The landmark survival estimates are presented in Table 52.

Table 52: Landmark survival rates from SPMs to the OS data for BSC

Distribution	Mean (months)	Median (months) (months)	OS (%) at landmark timepoints						
			1/4-year	1/2-year	1-year	3-year	5-year	30-year	40-year
Exponential	4.5	3.0	51%	26%	7%	0%	0%	0%	0%
Weibull	4.9	3.9	62%	30%	5%	0%	0%	0%	0%
Gompertz	4.7	3.4	57%	30%	5%	0%	0%	0%	0%
Log-logistic	4.9	3.7	61%	26%	5%	0%	0%	0%	0%
Log-normal	4.9	3.4	60%	26%	6%	0%	0%	0%	0%
Generalised gamma	4.9	3.4	60%	25%	6%	0%	0%	0%	0%

Abbreviations: BSC, Best supportive care; KM, Kaplan-Meier; OS, Overall survival; SPM, Standard parametric modelling.

Summary of base case survival analysis

The chosen distributions to inform the base case are presented in Table 53.

Table 53: Survival analysis approach and distributions used to inform the base case survival analysis

Clinical parameter	Selected base case model
PFS: Lifileucel	Log-normal MCM, adjusted for ipilimumab based on STC
PFS: Ipilimumab	Log-logistic
PFS: Chemotherapy	Log-logistic
PFS: BSC	Log-logistic
OS: Lifileucel	Exponential MCM, adjusted for ipilimumab based on STC
OS: Ipilimumab	Log-normal
OS: Chemotherapy	Log-normal
OS: BSC	Log-normal

Abbreviations: BSC, Best supportive care; MCM, Mixture cure modelling; OS, Overall survival; PFS, Progression-free survival; STC, Simulated treatment comparison.

3.3.2 Patients flow and discontinuation of the treatment in the C-144-01 trial

The participant flow of C-144-01 trial was described in Section 2.4 and presents how patients were classified in the trial through the different analysis sets (screened set, TH set, SAS, FAS and PDAwCS). The discontinuation rates represent the fraction of patients who were initially enrolled in the C-144-01 trial but ultimately did not receive lifileucel that was in-specification of the SmPC, this is further discussed in Appendix K.1.

The alive patients who did not receive lifileucel infusion that was in-specification of the SmPC were assumed to receive standard of care (ipilimumab, chemotherapy, BSC) based on market shares ([redacted] - ipilimumab, [redacted] – chemotherapy, [redacted] – BSC, further details in company BIA submission).

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.

3.3.3 Adverse events

Grade ≥3 AEs that occurred in ≥5% of patients for at least one of the treatments were included in the economic model. The data sources used for the AEs were the same as the efficacy data sources identified in Section 3.1 to keep consistency with the patient characteristics and clinical efficacy in the base-case analysis. Following previous appraisals in metastatic melanoma, an indirect comparison of safety profiles across lifileucel, ipilimumab and chemotherapy was not conducted. This is because the impact of AEs on the cost-effectiveness of lifileucel was expected to be minimal. For BSC, conservatively no adverse events were assumed. The values used are presented in Table 54.

Table 54: Incidence of Grade ≥3 adverse events included in the model

AEs	Lifileucel	Ipilimumab	Chemotherapy	BSC
Source for AE rates	C-144-01 trial[86]	Da Silva *et al*. (2021)[131], Clinical expert opinion[129]*	Mangin *et al.* (2021)[84]	NA
Thrombocytopenia	[redacted]	1.00%	1.76%	0.00%
Anaemia	[redacted]	1.00%	2.64%	0.00%
Febrile neutropenia	[redacted]	0.00%	0.00%	0.00%
Neutropenia	[redacted]	0.00%	1.32%	0.00%
Leukopenia	[redacted]	0.00%	0.00%	0.00%
Hypophosphatemia	[redacted]	0.00%	0.00%	0.00%
Lymphopenia	[redacted]	0.00%	0.00%	0.00%
Hypoxia	[redacted]	0.00%	0.00%	0.00%
Hypotension	[redacted]	0.00%	0.00%	0.00%
Pyrexia	[redacted]	0.00%	5.00%	0.00%
Hypertension	[redacted]	0.00%	5.00%	0.00%
Rash maculo-papular	[redacted]	1.00%	5.00%	0.00%
Increased alanine aminotransferase or aspartate aminotransferase	[redacted]	9.00%	0.00%	0.00%
Chills	[redacted]	0.00%	5.00%	0.00%
Diarrhoea or colitis	[redacted]	20.00%	0.00%	0.00%
Hypophysitis	[redacted]	5.00%*	0.00%	0.00%

*Clinical expert opinion stated to have 5% adverse event for hypophysitis in ipilimumab.[129]
Abbreviations: AE, Adverse event; BSC, Best supportive care; NA, Not applicable.

3.4 Measurement and valuation of health effects

Each health state in the model is associated with a specific utility weight, reflecting the impact of disease progression status on HRQoL. As detailed in Section 1.3, patients with metastatic melanoma typically experience worse HRQoL compared to the general population. In the base case, utility values for the health states PF and PD were sourced from various studies and precedence in published NICE technology appraisals. This approach was deemed appropriate as, although QoL data were collected in the C-144-01 trial, collection was not systematic and the data were not considered robust for use in NICE assessment compared to the phase 2 or phase 3 trials in the 2L+ melanoma that reported QoL outcomes (see Section 3.4.2). Sources of QoL data and the rationale for selection of the base case source are presented in sections below.

3.4.1 Health-related quality-of-life data from clinical trials

In the C-144-01 trial, the QoL of patients was assessed using the EORTC QLQ-C30 questionnaire. HRQoL scores were summarised at baseline, at week 12, Month 6, Month 12, and Month 24 for the FAS Pooled Cohorts 2 and 4 as presented in Section 2.6.4 with analyses taken from a 24 February 2022 data cut.[154]

3.4.2 Mapping

As the QLQ-C30 questionnaire does not directly yield utility values, mapping techniques were explored to approximate EQ-5D scores from QLQ-C30 responses. A systematic approach to identify and implement mapping algorithms was employed, the methods, selection criteria, selected model results and conclusions are provided in Appendix N.

Three models were selected, Versteegh *et al.* (2012), Kim *et al.* (2012) and Wojciechowski *et al*. (2022), and mapping conducted.[155–157] The assessment of data quality and sufficiency raised significant concerns regarding the completeness of the dataset, particularly given the relatively small study size and the nature of this endpoint as exploratory. Of 152 subjects that had at least one instance of QLQ-C30 questionnaire completed, 35 (23.03%) had only one visit, and 64 (34.87%) had only two visits, resulting in an inability to fully determine utility value changes over time. For subjects with more than two measurements, the overall average time between

visits was 131 days, and the overall Standard Deviation of time between visits was 110 days. These values further indicated that consistent calculation of utility changes over time from this study population would not be possible to derive from the available data.

Given these limitations in calculating utility changes over time with this dataset, summary statistics were calculated across the responses available to compare with published utility score values for this patient population.

The outputs of all three models were analysed and compared to each other and to values in the published literature. The Versteegh model outputs were deemed to be too implausible and an unrealistic fit as the model yielded a high number of negative utility values. Kim Model outputs were possible to calculate for a total of 417 visits/responses to the QLQ-C30 questionnaire. The mean utility score according to the Kim model was 0.88, the median was 0.92, and the values ranged from a minimum of 0.47 to 0.99. Wojciechowski Model outputs were possible to calculate for a total of 417 visits/responses to the QLQ-C30 questionnaire. The mean utility score was 0.73, the median was 0.80, and the values ranged from -0.16 to 0.98.

Comparing the outputs of this modelling exercise with published data, the utilities resulting from the Kim model are in range but more optimistic than the available published data. The published utility values were 0.82 for patients in a progression free state, 0.69 for those in a progressed state, and between 0.8 and 0.95 for those achieving cure, depending on patient age. The median values for both the Kim model and the Wojciechowski model are aligned with what is found in the literature.

While both models produced utility values within these ranges, the Kim model tended to produce higher utility values, aligning more closely with the utility values for progression-free state and cured subgroup. In contrast, the Wojciechowski model yielded lower estimates on average, with a broader distribution that produced more extreme values at the lower end, some of which may be implausible due to their negative values. These discrepancies were further evaluated (see Appendix N).

It was concluded that the available data were not sufficient to robustly calculate utility score changes over time. This limitation prevents meeting the standards required for

health economic modelling to NICE's standards. The dataset exhibited limitations in terms of completeness and follow-up intervals, reducing its suitability for direct longitudinal utility estimation. Given these constraints, published utility values were sourced from the literature and derived from validated methodologies to be used for economic modelling. This approach ensures alignment with NICE's expectations for health economic submissions, particularly regarding the reliability and generalizability of utility estimates.

However, outputs from two models indicate that the derived utility ranges in the C-144-01 study dataset closely matched utility scores found in the published literature, supporting the appropriateness of using published utility values for this population. This alignment reinforces confidence that the published values are applicable to this population and scenario.

3.4.3 Health-related quality-of-life studies

An SLR was undertaken in August 2024 and updated in January 2025 to identify published HRQoL studies relevant to the decision problem. The methods, search strategies and inclusion and exclusion criteria used, along with results for the SLR of the HRQoL studies are provided in Appendix F.

A total of 91 records were identified. Of these, 36 were selected for full text review, after screening of title and abstract. At full text review, 33 papers were excluded: five based on intervention/comparator, 19 based on population, and nine based on study type and outcomes. Three studies were selected for data extraction (see Table 55).

Table 55: Summaries of HRQoL studies included in the SLR

Reference	Study design	Population	Instrument	Summary of outcomes
Ten Ham et al. (2024)	Prospective cost-utility analysis based on multicentre, open-label, randomized, phase 3 clinical trial (Denmark,	Unresectable stage IIIC-IV melanoma after failure of first-line or second-line treatment	EQ-5D-3L	**Stable disease (baseline):** • Ipilimumab 0.874 • TIL-NKI/CCIT: 0.879 **Progressive disease:** • Ipilimumab (rechallenge): 0.764 • Ipilimumab/nivolumab combination therapy: 0.695

	the Netherlands)			• BRAF/MEK inhibitor: 0.844 • Pembrolizumab: 0.707 • Temozolomide: 0.730 • Dacarbazine: 0.791 • No treatment after TIL-NKI/CCIT: 0.832 • No treatment after ipilimumab: 0.764
Retèl *et al.* (2018)	Early cost-effectiveness model based on a hypothetical cohort of patients, in the setting of the Netherlands.	Previously treated metastatic melanoma (stage IV) was simulated, starting at age 52. Specific previous treatment not listed.	Standard gamble (sourced from Beusterien *et al*. [2009])	Stable disease: 0.850 Progressive disease: 0.590
Schadendorf *et al*. (2024)	PROs assessed using 7.5 year follow-up data from phase 3 clinical trial (CheckMate-067).	Previously untreated, unresectable, or metastatic melanoma.	EQ-5D-3L	Progression-free disease: 0.780 Progressive disease utility value: Not reported

Abbreviations: EQ-5D, EuroQol-5 Dimension; PRO, Patient reported outcome; MEK, Mitogen-activated extracellular signal-regulated kinase; NCT, National Clinical Trial; TIL-NKI/CCIT, Tumour-Infiltrating Lymphocytes from the Netherlands Cancer Institute/Center for Cancer Immune Therapy.

In addition to the studies identified by the SLR, previous melanoma TAs for both first-line and second-line treatments were assessed to supplement outcomes, with 12 previous melanoma TAs and one guideline being extracted (see Table 56).

Table 56: Previous melanoma technology assessments published by NICE

NICE TA	Year	Title	Line	Progression-free	Progressed	Study	Instrument
TA268	2011	Ipilimumab for previously treated unresectable malignant melanoma	2	0.80 (for all treatment arms)	0.76 (for all treatment arms)	MDX010-20	EQ-5D
TA269	2012	Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma	2	• Vemurafenib 0.81 • Dacarbazine 0.77	0.59 (for all treatment arms)	Beusterien *et al*. (2009), Nafees *et al.* (2008)	Standard Gamble
TA319	2014	Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma	1	• Placebo + DTIC 0.85 • Ipilimumab + DTIC 0.84	• Placebo +DTIC 0.84 Ipilimumab + DTIC 0.83	CA184-024	EORTC QLQ-C30
TA321	2014	Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma	2	• Dabrafenib 0.77 • Vemurafenib 0.77 • Dacarbazine 0.75	0.68 (for all treatment arms)	BREAK-3	EQ-5D
TA357	2015	Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab	2	• MK3475 2mg 0.75 • Chemotherapy 0.73	• MK3475 2mg 0.69 • Chemotherapy 0.68	KEYNOTE-002	EQ-5D
TA366	2015	Pembrolizumab for advanced melanoma not previously treated with ipilimumab	1	• MK3475 10mg 0.81 • Ipilimumab 0.77	• MK3475 10mg 0.71 • Ipilimumab 0.68	KEYNOTE-006	EQ-5D
NICE guidelines NG14	2015	N/A	N/A	0.80	0.69	Average source from TA562, TA400, TA396,	EQ-5D

						TA384, TA366 and TA357	
TA384	2016	Nivolumab for treating advanced (unresectable or metastatic) melanoma	1	• Pre-progression + days left ≥ 30: 0.8018 • Pre-progression + days left < 30: 0.7795 (For all treatment arms)	• Post-progression + days left ≥ 30: 0.7277 • Post-progression + days left < 30: 0.7054 (For all treatment arms)	CheckMate066	EQ-5D
TA396	2016	Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma	2	• Trametinib + dabrafenib 0.84 • Vemurafenib 0.75 • Dabrafenib 0.79	0.70 (For all treatment arms)	COMBI-d, COMBI-v	EQ-5D
TA400	2016	Nivolumab in combination with ipilimumab for treating advanced melanoma	1	0.80 (For all treatment arms)	0.76 (For all treatment arms)	Checkmate 067	EQ-5D
TA410	2016	Talimogene laherparepvec for treating unresectable metastatic melanoma	1	0.77 (For all treatment arms)	0.68 (For all treatment arms)	BREAK-3 (sourced from TA321)	EQ-5D
TA562	2019	Encorafenib with binimetinib for unresectable or metastatic BRAF V600 mutation-positive melanoma	2	• Encorafenib + binimetinib 0.78 • Dabrafenib + trametinib 0.80	0.68 (For all treatment arms)	COLUMBUS	EQ-5D
TA950	2024	Nivolumab-relatlimab for untreated unresectable or metastatic melanoma	1	ND*	ND*	RELATIVITY-047	EQ-5D

*Values were redacted.
Abbreviations: EQ-5D, EuroQol-5 Dimension; N/A, Not applicable; ND, Not disclosed; TA, Technology assessment

3.4.4 Health-related quality of life data used in the cost-effectiveness analysis

To evaluate the overall quality-adjusted life years associated with each treatment in the model, utility values are assigned to each health state (e.g. PF and PD) and applied to the proportion of patients in that state for the duration of each cycle. These values are also age-adjusted to account for the natural decline in utilities over time. A summary of the health state utility values used within the economic model is provided in Table 57.

Given that the C-144-01 trial's QoL data were not systematically collected post-event of the trial, they were considered unsuitable for use in the model due to limited data availability, as outlined in Section 3.4.2. Consequently, utility estimates for the PF and PD health states were derived from various publications and previous NICE submissions. Notably, the utility values collected and mapped in C-144-01 trial did not substantially differ from the reference utility values used for our modelling purposes. The utility values for PF and PD states were calculated as simple averages across selected studies based on the relevance of their QoL data to the 2L and 3L+ setting, for example, 1L post-progression utilities for PD-1s were used to inform the 2L progression free average utility.

For chemotherapy and BSC, as no long-term survivors were assumed, utility values from the literature for the PF and PD health states were applied to the proportion of patients in that state, throughout the time horizon.

For lifileucel and ipilimumab in the base case, utility values for the PF and PD health state sourced from literature were applied for the first 3 years. After 3 years, patients who remained in PF health state transitioned to age- and gender-matched general population utilities for the UK, which were based on Hernandez et al. (2022).[158] This approach aligned with the methodology adopted in NICE TA872 and TA649, and was based on the clinical experts opinion who stated that the cured subgroup who are also referred to as (i.e. long-term survivors) are expected to experience minimal disruption in their quality of lives compared to general population.[16,118,159] A scenario analysis was also conducted to explore the impact of an alternative time point for cure when PF patients start to experience the general population utilities (5 years, Section 3.9).

For patients who remained in PD health state, the utility values were not adjusted according to cure status as cure rates were derived from the PFS data under the assumption that cured patients are free of disease progression and risk of disease related death.

Utility estimates for lifileucel, ipilimumab, chemotherapy and BSC were extracted from the sources listed in Table 55 and Table 56. The utility values for PF and PD states were calculated as averages, selected based on their relevance to previously treated and untreated metastatic melanoma. TAs and literature for both first-line and second-line treatments were identified as outlined in Section 3.4.3.

In the model, the PF utility value was calculated as the average of PF utility values from second-line appraisals and PD utility values from first-line appraisals. Given that lifileucel is considered a second-line treatment, PF utility values from NICE TAs and literature of first-line treatment were not considered to be relevant. However, PD utility values of first-line treatments were assumed to be equivalent to the PF utility values for second-line treatment. Therefore, the PD utility value in the model was derived as the average of PD utilities across second-line appraisals only. Utility values used in the CEM from NICE TAs for the PF health state were sourced from NICE TA268, TA269, TA319, TA321, TA357, TA366, TA384, TA396, TA400 and TA562, while those for PD were sourced from TA268, TA269, TA321, TA357, TA396 and TA562.[68–71,73–78] The utility values for each NICE TA are presented in Table 56.

Utility values from Retel *et al.* (2018) were also considered appropriate as it is a cost-effectiveness study of TIL versus ipilimumab for second line of treatment in advanced melanoma patients. The utilities allocated to the health states were adapted from Beuesterien *et al.* (2009) that used standard gamble approach to derive utilities elicited from 140 respondents in the United Kingdom and Australia.[160] According to UK clinical experts, the utility values used in Retel *et al.* (2018) were generally consistent with their clinical experience. However, the panel expected a larger gap between PF and PD utility values, with a higher PF utility value.[16]

Additionally, utility values from the ten Ham *et al.* (2022) study were included in the analysis as it is a cost-effectiveness study of treating advanced melanoma with ex vivo-expanded TIL from autologous melanoma tumour, compared with ipilimumab

after failure of first-line or second-line treatment. Treatment specific utilities for the PF health state were derived from the EQ-5D-3L data. For patients continuing to a next line of treatment, a treatment-specific utility was extracted from literature.[111] The PD utility values from this study were averaged across treatment arms and utilised in the economic model as the PF utility value.

A summary of the health state utility values used within the economic model were provided in Table 57. The same PF and PD utility values were applied to all interventions (lifileucel, ipilimumab, chemotherapy, BSC), similar to the approach used in advanced melanoma NICE appraisals, TA268, TA384, TA400 and TA410.[73,77,78,114] A scenario analysis was also conducted to explore the impact of sources with the highest and lowest PF utility values, specifically Retel *et al*. (2018) and TA357 respectively (Section 3.10).[70,110] Only studies with both available PF and PD utility values were considered for the scenario analysis.

Table 57: Summary of health state utility values for cost-effectiveness analysis base-case

Health state	Utility value: mean (standard error)	95% confidence interval*	Source
PF (for all treatment arms)	0.77 (0.155)	(0.409, 0.983)	Average utility values estimated from TA268, TA269, TA321, TA357, TA366, TA384, TA396, TA400, TA562 Retel *et al.* (2018) and Ten Ham *et al*. (2024).
PD (for all treatment arms)	0.67 (0.134)	(0.385, 0.895)	

Abbreviations: PD, Progressed disease; PF, Progression-free, TA, Technology assessment, NICE, National Institute of Health and Care Excellence.
*The 95% confidence interval was calculated using beta distribution with 20% SE assumed.

3.4.5 Age-adjusted utilities

An age-related adjustment on the utility scores were included in the base-case to account for the deterioration in HRQoL with age. The age-related adjustment was applied to the health state in each cycle for the duration of the time horizon using methods described in Hernandez-Alava *et al.* (2022), which is in line with the NICE reference case.[123,158] The utility values decrease with age, reflecting a decline in HRQoL over time. However, this decrease is not constant per year, with varying rates of decline. The decline in utility is minimal during childhood and early adulthood,

accelerates through midlife and steepens after age 70. Between ages 60 and 70, utility values decreased by approximately 0.0037 per year and the rate of decline accelerates slightly between ages 70 to 80, with utility values dropping by about 0.0045 per year. Additionally, the adjustment was gender-specific, with males generally having higher utility scores than females at every age. The relative utility scores were also adjusted in comparison to the base age of [redacted] with younger individuals having a higher utility relative to older patients.

3.4.6 Disutilities due to lifileucel administration

A modest utility decrement related to lifileucel administration was derived and applied to the economic model to reflect the potential disutility of lifileucel's administration procedure on patient's QoL. UK clinicians indicated that measurements of QoL data in C-144-01 trial at baseline and Week 12 would not adequately capture the short-lived decrement in QoL expected with lifileucel administration, notably for those patients who require an ICU stay. To estimate this decrement, treatment-related disutility and utility in the event-free state related to CAR-Ts administration was used as a proxy. In the NICE TA975 (Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years), a disutility of 0.42 was assumed for the tisagenlecleucel administration, and 0.91 utility was assumed for the event-free survival. Based on these two values, a proportional decrease in utility due to treatment administration compared to event-free survival was estimated at 46%. The ratio of the treatment-related disutility to utility in the event-free state in the CAR-T appraisal was assumed to be identical to the ratio of lifileucel-related disutility to utility in the PF state. This proportional utility decrement compared to PF utility was assumed for lifileucel patients who required an ICU stay post-lifileucel administration (20% of patients, based on UK clinical experts).[121,129] Based on this approach a 0.09 (46% multiplied by 20%) disutility was estimated to be associated with lifileucel administration. This disutility was applied in the first cycle of the lifileucel arm in a one-off fashion.

3.4.7 Adverse events disutilities

Utility decrements associated with adverse events were sourced from published literature and incorporated into the cost-effectiveness model as presented in Table 58.

Utility decrements were multiplied by the incidence rates of each AE (Table 54) for each intervention and summed. The aggregate disutility associated with AEs was subsequently applied as one-off disutility in the first model cycle for each treatment. This one-off application of aggregate disutility of AEs in the first cycle was for simplicity and according to the assumption that AEs occur soon after treatment initiation and only require acute care. The assumption was based on TEAEs observed in Cohort 4, where a dramatic decrease was seen within the first two weeks following lifileucel infusion.[86] The same one-off disutility application approach was also applied in the *de novo* economic modelling of the NICE guideline for melanoma: assessment and management (NG14) and TA950 (in the company's alternative modelling following the EAG comment).[10,115]

Table 58: Utility decrements associated with adverse events

Adverse event	Disutility	Source
Thrombocytopenia	0.09	TA893, Nafees *et al.* (2017)[119,162]
Anaemia	0.09	Beusterian *et al.* (2010)[160]
Neutropenia	0.09	TA893, Nafees *et al.* (2017)[119,162]
Lymphopenia	0.09	Assumed to be equal to neutropenia
Leukopenia	0.09	TA893, Nafees *et al.* (2017)[119,162]
Febrile neutropenia	0.09	TA893, Nafees *et al.* (2017)[119,162]
Hypophosphatemia	0.07	TA893, TA783[119,163]
Hypoxia	0.22	Lachaine *et al*. (2015)[164]
Hypotension	0.07	TA893, TA783
Pyrexia	0.11	Beusterian *et al*.(2010)[160]
Hypertension	0.07	TA893. Assumed to be equal to hypotension[119]
Rash maculo-papular	0.03	Paly *et al.* (2020), TA950[112,115]
Chills	0.11	Assumed to be equal to pyrexia
Diarrhoea or colitis	0.01	Beusterian *et al.* (2010), TA950, TA384[78,115,160]
Increased alanine aminotransferase or aspartate aminotransferase	0.05	TA950, Barbier *et al.* (2022)[115,165]
Hypophysitis	0.13	Middleton *et al*. (2017)[166]

Abbreviations: TA, Technology assessment.

3.5 Cost and healthcare resource use identification, measurement and valuation

A healthcare cost and resource use (HCRU) SLR was conducted in August 2024 and updated in January 2025 to investigate the costs and resource use associated with

the management of adult patients with unresectable or metastatic, previously treated melanoma, following the PICOS (population, intervention, comparators, outcomes, and study type) principle[167]. The methods, search strategies, inclusion and exclusion criteria used, along with results for the SLR of the HCRU studies are provided in Appendix G.

A total of 840 records were identified from Embase. A total of 742 records were excluded following screening of titles and abstracts. The remaining 98 records were selected for full-text review. At full-text review, 90 studies were excluded: two based on intervention/comparators, 14 based on population and 74 based on study type and outcomes. Overall, a total of eight records were selected for data extraction, and an additional five TAs of relevance were identified in the "grey" searches. See Appendix G for a complete list of all extracted papers.

3.5.1 Intervention and comparators' costs and resource use

For all interventions, drug acquisition and administration costs were included in the model. For lifileucel, any additional pre- and post-treatment costs were also included.

Drug acquisition costs were calculated based on the recommended dosing regimen for each treatment as briefly discussed in Section 3.2.3 and detailed further in the sections below. Unit costs were obtained from either the Drugs and Pharmaceutical Electronic Market Information Tool (eMIT) or the BNF, and the lowest price was assumed.[168,169] In instances where multiple pack prices were available, the pack price with the lowest cost per milligram (mg) was used.

Where applicable, drug administration costs were applied to treatments administered intravenously (IV) or orally for the duration of treatment in each treatment arm. Oral administration costs were considered only for some chemotherapy treatments, to cover any additional monitoring and supervision. For lifileucel treatment, the administration costs were assumed to be included during patients' hospital stay. The unit costs for the drug administration were based on the National Schedule of NHS Costs 2023-2024, as presented in Table 59.[170]

Table 59: Drug administration costs

Description of cost	Unit cost (£)	Source
Oral administration	283.17	SB11Z – Deliver exclusively oral chemotherapy
Complex intravenous infusion (first attendance)	508.97	SB13Z – Deliver more Complex Parenteral Chemotherapy at First Attendance
Intravenous infusion (subsequent)	430.24	SB15Z - Deliver Subsequent Elements of a Chemotherapy Cycle

Source: National Schedule of NHS Costs, 2023/24[170]

3.5.1.1 Dosing

Relative dose intensity (RDI)

Dosing adjustments, including dose reductions and delays, were accounted for in the model by incorporating relative dose intensity (RDI). The RDI reflects the actual dose received by patients relative to the recommended dose in the administration schedule. To model these adjustments, the RDI values were applied by multiplying the RDI by the recommended dose specified in the treatment schedule.

Wastage

For treatments where dosing is based on weight or BSA (ipilimumab, chemotherapy, pre- and post-lifileucel treatments), the model has a functionality to include or exclude drug wastage. In the model's base case, wastage is included, while a no wastage scenario was analysed in a separate analysis.

The dose for each intervention or comparator is adjusted by RDI regardless of wastage. Wastage was not assumed for lifileucel infusion as the dose is specifically manufactured to be infused fully. In the absence of drug wastage, the acquisition costs were calculated by multiplying the price per vial/tablet (obtained from the eMIT or BNF) by the exact number of vials/tablets needed for each dose.

When wastage is assumed, the dosing was calculated based on the method of moments (MoM), using baseline patient body surface area (BSA) or baseline patient weight to estimate the mean number of vials/tablets required and the associated cost per cycle, utilising patient level data from the C-144-01 trial.

Method of methods (MoM) is an established methodology used in economic modelling that uses patient's weight or BSA dosing scheduled to derive more accurate estimates

of drug costs. Without MoM, a single dose per patient is calculated as a dose from the SmPC multiplied by average weight/BSA, with wastage calculated through comparison to the nearest vial size. However, this method of calculation does not account for weight/BSA variation within the patient population. MoM takes into account how weight/BSA is distributed across the patient population to calculate a range of doses that are used depending on weight/BSA ranges, so wastage is more accurately calculated.

The MoM uses the patients' weight and body surface area from the C-144-01 trial, to determine distributions of doses that are used in the patient population and calculate wastage for a single dose. The MoM calculations assume the patient's BSA and weight follow a log-normal distribution, therefore, the dose patients receive per cycle is also assumed to be log-normally distributed. For every possible dose the number of vials/tablets required for each dose is calculated and rounded up. For each dose, costs of vials/tablets are weighted by multiplying the cost of vials/tablets by the distribution of each dose. The total acquisition cost per administration is then derived by the sum of the weighted costs per vial/tablet. An example of the calculations included in the CEM is presented in Table 60.

Table 60: Cisplatin (50mg/m2 dose) method of moments example calculation

Total dose per patient (mg)	Distribution	Number of 10 mg vials	Number of 50 mg vials	Number of 100 mg vials	Cost of all vials (£)	Weighted cost of vials
70	0.01	2	1	0	30.96	0.27
80	0.07	3	1	0	34.19	2.53
90	0.22	4	1	0	37.42	8.24
100	0.30	0	0	1	29.27	8.81
110	0.23	1	0	1	32.50	7.47
120	0.11	2	0	1	35.73	4.04
130	0.04	3	0	1	38.96	1.55
140	0.01	4	0	1	42.19	0.58
Total weighted cost per admin						33.48
Total weighted cost per cycle (3 administration per cycle)						100.43

Note: The cost of vials are calculated through multiplying the number of each vials by the unit cost of each vial. The weighted cost of vials is calculated by multiplying the distribution percentage by the cost of vials. The total weighted cost is the sum of the weighted cost of vials.

MoM was implemented to allow for greater accuracy when calculating dosing, and robustness to outliers, such as patients who require substantially higher doses due to their weight or BSA being higher, compared to the average patient.

3.5.1.2 Lifileucel treatment costs

Some patients may discontinue in the process leading up to lifileucel infusion due to adverse event, death or receiving out-of-specification lifileucel dose, as detailed in Section 3.3.2.[86] Given the variability in the timing of patient discontinuation, different cost allocations were applied to patients depending on their specific treatment pathway. The costs were calculated by accounting for the percentage of patient flow through various stages of the treatment, between assignment to lifileucel and receiving lifileucel infusion (Table 61). Each of these proportions was subsequently multiplied by the proportion of patients expected to accrue costs at each step of the treatment pathway, as shown in Table 61.

Table 61: Percentage of lifileucel patients who will accrue different costs

Cost component	% of patient who will accrue costs							
	Patients who will accrue costs but die between tumour harvest and receiving lifileucel	**Source**	**Patients who will accrue costs but discontinue between tumour harvest and receiving lifileucel**	**Source**	**Patients who will receive lifileucel infusion that is out-of-specification**	**Source**	**Patients who will receive lifileucel infusion that meet specification**	**Source**
Tumour tissue procurement	100%	Based on the assumption that all patients undergo tumour procurement	100%	Based on the assumption that all patients undergo tumour procurement	100%	Based on the assumption that all patients undergo tumour procurement	100%	Clinical pack[86]
LD regimen	0%	Assumption**	[redacted]	Clinical pack[86]*	100%	Assumption**	100%	Clinical pack[86]
Lifileucel infusion	0%	Assumption that the NHS will only pay for lifileucel that will be administered and meet dose specification.	0%	Assumption that the NHS will only pay for lifileucel that will be administered and meet dose specification.	0%	Assumption that the NHS will only pay for lifileucel that will be administered and meet dose specifications.	100%	Clinical pack[86]
Post-lifileucel infusion	0%	Assumption	0%	Assumption that patients who received lifileucel will incur post-lifileucel cost	[redacted]	Assumption that patients who received lifileucel will incur post-lifileucel cost.	[redacted]	Clinical pack[86]

*For pooled Cohorts 2 and 4, of the [redacted] patients who received LD in the TH set ([redacted]), 156 patients received lifileucel in the SAS. Therefore, the proportion of [redacted] is expected to accrue LD regimen costs although they will discontinue before receiving lifileucel.

** Assumed that for out-of-SmPC-specification doses of lifileucel, clinicians will prefer to have it administered and that all patients will receive LD before receiving out-of-SmPC-specification dose.
Abbreviation: CSR, Clinical study report; NHS, National Health Service; LD, lymphodepletion; SAS, Safety analysis set; TH, Tumour harvested.

The acquisition and administration costs associated with lifileucel infusion; including the pre-treatment and post-treatment costs, were applied as a one-off cost in the first cycle of the model, as described in the following sections. No acquisition cost was assumed for patients who will receive an out-of-SmPC-specification dose since there is no charge for a product that does not meet the SmPC dose range of between 7.5 to 72 billion cells.

The pre- and post-treatment administration costs of lifileucel treatment, included both hospitalisation and ICU costs. Hospital resource use data collected and summarised for the FAS of Cohort 4 (N=87) was used to inform the median number of days in hospital; this data was unavailable for Cohort 2.

Lifileucel pre-treatment cost

Lifileucel therapy is associated with costs prior to receiving lifileucel infusion. The associated pre-treatment costs are for tumour tissue procurement surgery and the LD regimen.

Tumour tissue procurement

Based on the C-144-01 clinical pack, 100% of patients enrolled underwent tumour tissue procurement as part of the treatment protocol.[86] As detailed in Section 1.2, the production of lifileucel involves the surgical resection of a patient's tumour, which may originate from either a primary or metastatic lesion and is integral for the manufacturing of lifileucel.

The distribution of the tumour resection sites, categorised by anatomical location, is presented in Table 62.

Table 62: Resected Tumour Site for Pooled Cohorts 2 and 4

Resected Tumour Site	n (%)
Lymph Node	[redacted]
Other*	[redacted]
Skin/Subcutaneous	[redacted]
Lung	[redacted]
Liver	[redacted]
Peritoneal/Retroperitoneal	[redacted]
Other Visceral	[redacted]

Breast	[redacted]
Musculoskeletal	[redacted]
Total	[redacted]

Source: C-144-01 clinical pack[86]
*Resected tumour sites were provided by patient and only one resection site was used per patient.

The costs of the tumour procurement were assumed to be captured by the daily hospital costs, which were sourced from the NHS 2023/24 reference costs and estimated using elective inpatient codes based on the resection site.[170] The inpatient tumour procurement costs are detailed in Table 63.

Table 63: Inpatient tumour procurement costs

Site of resection	Unit cost (£)	Source
Lung	1,341.62	Reference code YD03Z. Elective inpatient: Percutaneous Biopsy of Lesion of Lung or Mediastinum.
Lymph node	6,202.05	Reference code WH54A-B. Elective inpatient: weighted average of Procedures on the Lymphatic System with CC Score 0 and 1+. The reference codes were sourced from NICE TA837.[171]
Liver	1,315.96	Reference codes YG10Z and YG11A. Elective inpatient: Weighted average of Percutaneous Transvascular Biopsy of Lesion of Liver and Percutaneous Punch Biopsy of Lesion of Liver, 19 years and over.
Musculoskeletal	1,907.78	Reference codes YH31A and YG11A. Elective inpatient: weighted average of Percutaneous Biopsy of Lesion of Bone, 19 years and over and Percutaneous Biopsy of, Lesion of Muscle or Connective Tissue, 19 years and over.
Skin/ subcutaneous	2,618.61	Reference code JC42C Elective inpatient: Intermediate Skin Procedures, 19 years and over. The reference codes were sourced from NICE TA837.[171]
Breast	1,263.61	Reference code YJ09Z Elective inpatient: Vacuum Assisted Biopsy or Excision of Lesion of Breast.
Peritoneal/ Retroperitoneal	1,273.44	Reference code YL20A Elective inpatient: Percutaneous Needle Biopsy of Lesion of Kidney, 19 years and over.
Other Visceral	2,597.49	Due to the absence of data, the average of all the mentioned reference codes for tumour procurement has been applied.
Other	2,597.49	Due to the absence of data, the average of all the mentioned reference codes for tumour procurement has been applied.

Source: National Schedule of NHS Costs - Year 2023/24.[170]
Abbreviations: NHS, National Health Service; NICE, National Institute for Health and Clinical Excellence.

The average daily cost of tumour resection was determined by calculating the weighted average of inpatient costs across all tumour resection sites (by multiplying the proportion of patients at each resected site by the corresponding inpatient cost associated with the site and summing the results across all sites), which resulted in a

total daily inpatient cost of £1,737.70. For tumour tissue procurement for lifileucel, the median length of inpatient stay assumed in the model was [redacted].[86] Therefore a cost of [redacted] for the total length of stay related to tumour tissue procurement was assumed. This cost was applied as a one-off cost in the first cycle of the model.

LD regimen

The model estimates the costs of the LD regimen prior to administration of lifileucel. The median number of hospitalisation days related to the LD regimen was [redacted], which was applied to the model.[86]

The costs of the LD regimen included drug acquisition and administration costs of cyclophosphamide, mesna and fludarabine. The dosing regimen, unit costs and acquisition cost for each drug are detailed in Table 64 and Table 65. The RDI for cyclophosphamide and fludarabine were sourced from the C-144-01 clinical pack, whilst the RDI for mesna was assumed 100% due to absence of data.[86] The treatment acquisition cost per cycle (including RDI), with and without wastage, for each treatment is shown in Table 66.

Table 64: Dosing regimen of the LD treatments included in the economic model

Treatment	Dosing regimen	Source
Cyclophosphamide	60mg/kg IV with mesna daily for 2 days	C-144-01 clinical pack[86]
Mesna	Total dose of mesna is 60% of the oxazaphosphorine (cyclophosphamide) dose	Mesna SmPC[134]
Fludarabine	25mg/m^2 IV daily for 5 days	C-144-01 clinical pack[86]

Abbreviations: IV, Intravenous; mg, milligram, m; metre; SmPC, Summary of product characteristics.

Table 65: Unit cost of LD regimen

Treatment	Dosage strength (mg)	Pack size/vial volume	Administration route	Cost per pack (£)	Source
Cyclophosphamide	500.00 1000.00 2000.00	1.00 1.00 1.00	IV	8.21 15.22 28.22	BNF 2025[172]
Mesna	400.00 1000.00	15.00 15.00	IV	217.12 465.50	eMIT 2024[168]
Fludarabine	50.00	1.00	IV	105.93	eMIT 2024[168]

Abbreviations: IV, Intravenous; LD, Lymphodepletion; mg, Milligram.

Table 66: Acquisition cost of LD regimen

Treatment	Dose per administration (mg)	Administration per treatment cycle	Treatment cycle	RDI	Cost per cycle (£) – no wastage	Cost per cycle (£)* - wastage
Cyclophosphamide	4,857.78	2	Cycle 1 (Day 1 and 2)	98.24%	134.67	143.78
Mesna	2,914.67	2	Cycle 1 (Day 1 and 2)	100.00%	180.90	201.34
Fludarabine	49.00	5	Cycle 1 (Day 1 to 5)	87.43%	453.38	594.47

Abbreviations: mg, Milligram; RDI, Relative dose intensity.
*Note: The cost of wastage per cycle was calculated using the MoM to estimate the number of vials/tablets required in the base case, accounting for wastage and assuming no vial/package sharing occurs.

It was assumed that all patients who would receive lifileucel infusion, regardless of whether it met the dose manufacturing specifications, would receive pre-lifileucel LD regimen and accrue costs associated with the administration and acquisition of LD regimen. These costs were presented in Table 61. For patients who did not receive lifileucel infusion (either due to treatment discontinuation or death), [redacted] of these patients are expected to accrue LD regimen costs. This proportion was derived based on the pooled Cohorts 2 and 4, where [redacted] patients in the TH set discontinued and did not receive the lifileucel infusion.

As the LD regimen is administered in the inpatient setting, the drug administration costs were assumed to be captured in the cost of a hospital stay.

The daily hospital costs were sourced from the NHS 2023/24 reference costs described in Table 67.[170] Skin disorder codes were used as a proxy due to the unavailability of specific codes for melanoma.

Table 67: Inpatient costs for LD regimen

Input	Value	Source
Weighted average daily hospitalisation - unit cost (£)	535.33	Reference codes JD07A-JD07K, weighted day case cost. National Schedule of NHS Costs - Year 2023/24[170]
Length of hospital stay	[redacted]	C-144-01 clinical pack[86]
Total (£)	[redacted]	Calculation – length of hospital stay multiplied by the unit cost

Abbreviations: LD, Lymphodepletion; NHS. National Health Service.

Lifileucel acquisition and administration cost

The cost of a single, one-time infusion of lifileucel is [redacted] at list price and [redacted] at PAS price.

As outlined in Table 9, [redacted] of patients from the PDAwCS who have the tumour tissue procurement are expected to receive lifileucel infusion. The administration of lifileucel was assumed to require an average hospital stay of one day for infusion, based on the data reported in the C-144-01 clinical pack.[86]

The daily hospital costs were sourced from the NHS 2023/24 reference costs.[170] The administration cost of lifileucel treatment was presented in .

Table 68: Administration cost of lifileucel treatment

Hospital setting	Cost (£)	Proportion	Number of days	Total cost (£)	Source
Inpatient	535.33	[redacted]	[redacted]	[redacted]	Reference codes JD07A-JD07K, weighted day case cost.

Source: National Schedule of NHS Costs - 2023/24[170]
*[redacted] of patients from the PDAwCS who remained in the study and received lifileucel infusion were assumed to accrue inpatient costs.

Lifileucel post-treatment cost

The model included the costs of IL-2 regimen following the administration of lifileucel. IL-2 is administered 3 to 24 hours post-lifileucel infusion at a dose of 600,000 IU/kg every 8 to 12 hours, with a maximum of 6 doses over approximately 3 days as reported in the C-144-01 clinical pack.[86] The unit cost of IL-2 is listed in Table 69. The RDI value of IL-2, sourced from the C-144-01 clinical pack, was applied by multiplying the RDI by the dose recommended in the administration schedule.[86] The treatment costs per dose (including RDI) of IL-2, with and without wastage, were shown in Table 70.

The model also accounted for the extended hospitalisation days following IL-2 administration to reflect the potential costs associated with monitoring and/or IL-2-related adverse events. This length of stay is defined as the duration from IL-2 administration until the patient is discharged from the hospital. The numbers of inpatient and ICU days were informed by UK clinicians, who provided estimates of length of stay ranging from 5 to 12 days.[16] Specifically, they assumed that 20% of patients would require ICU admission and 80% would be managed in a general ward.[16]

In the base case scenario, the model adopted a conservative estimate of 10 hospitalisation days, comprising 2.0 days in the ICU and 8.0 days on a general ward.[16]

The daily general ward and ICU costs were sourced from the NHS 2023/24 reference costs using the codes JF07A-K and XC01X-Z, respectively.[170] The calculated inpatient and ICU costs for post-administration of lifileucel were shown in Table 71.

Table 69: Unit cost of IL-2

Treatment	Dosage strength	Pack size/vial volume	Administration route	Cost per pack (£)	Source
IL-2	18,000,000 IU	1	IV	636.00	BNF 2025[173]

Abbreviations: BNF, British National Formulary; IL-2, Interleukin-2 (Aldesleukin); IU, International unit; IV, Intravenous.

Table 70: Acquisition cost of IL-2

Treatment	Dose per admin (IU)	Treatment cycle	RDI	Cost per cycle (£) – no wastage	Cost per cycle (£)* - wastage	Number of admin per treatment cycle
IL-2	48,577,810.42	Cycle 1 (Day 1 up to Day 5)	97.71 %	10,062.66	11,448.00	6

Abbreviations: IL-2, Interleukin; IU, International unit; MoM, Method of moments; RDI, Relative dose intensity.
*Note: The cost of wastage per cycle was calculated using the MoM to estimate the number of vials required in the base case, accounting for wastage and assuming no vial sharing occurs.

Table 71: Inpatient and ICU costs for post-administration of lifileucel

Input		Source
Weighted average daily hospitalisation cost - unit cost (£)	535.33	Reference codes JD07A-JD07K, weighted day case cost. National Schedule of NHS Costs - Year 2022/2023[170]
Weighted average daily ICU cost - unit cost (£)	2,276.65	Reference codes XC01X-XC07Z, weighted day case cost. National Schedule of NHS Costs - Year 2022/2023[170] Based on TA893.[119]
Length of hospital stay	10 days • 2.0 days in the ICU • 8.0 days in the general ward	Clinical expert opinion[129]
Total cost (£)	8,835.92	Calculated based on unit costs and length of stay

Abbreviations: ICU, Intensive care unit; NHS, National Health Service.

3.5.1.3 Ipilimumab treatment cost

As described in Section 3.2.3.2 the recommended dose of ipilimumab is 3mg/kg administered intravenously over a 30-minute period every 3 weeks for a maximum of 4 doses.[77,135] However, the model assumed a mean dose of 3.6 in the base case as not all patients are expected to receive the full four maximum doses due to disease progression or toxicity concerns. This assumption was based on weighting the number of doses from the MDX-010 study by Hodi *et al*. (2010), which was validated by UK clinical expert as described in section 3.2.3.2.[16,174]

The unit cost of ipilimumab in different vial options was listed in Table 72. The RDI value of ipilimumab was assumed 100% due to the absence of data.[86] The treatment acquisition costs per dose (including RDI) of ipilimumab, with and without drug wastage, were shown in Table 73. The cost of wastage was calculated using MoM.

Table 72: Unit costs of ipilimumab

Treatment	Dosage strength	Pack size/vial volume	Administration route	Cost per pack (£)	Source
Ipilimumab	50mg	1	IV	3,750.00	BNF 2025[175]
	200mg	1	IV	15,000.00	BNF 2025[175]

Abbreviations: BNF, British National Formulary; IV, Intravenous; mg, Milligram.

Table 73: Acquisition cost of ipilimumab

Treatment	Dose per admin (mg)	Number of admin per treatment cycle	RDI	Cost per cycle (£) – no wastage*	Cost per cycle (£)** – wastage*	Number of treatment cycles
Ipilimumab	242.89	1	100.00%	18,216.68	20,070.39	3.6

Abbreviations: mg, milligram; MoM, Method of moments; RDI, Relative dose intensity.
* The cost per cycle reflects the cost of one full treatment cycle.
** The cost of wastage per cycle was calculated using the MoM to estimate the number of vials required in the base case, accounting for wastage and assuming no vial sharing occurs.

3.5.1.4 Chemotherapy treatment cost

The chemotherapy comparator in the model comprised of a basket of chemotherapy treatments; dacarbazine only, temozolomide only, carboplatin only, carboplatin + paclitaxel and dacarbazine + cisplatin with weightings for each treatment as shown in Table 74, Section 3.2.3.3. All chemotherapy treatments except temozolomide, which is administered as an oral tablet, are administered via intravenous infusion. The cost

per administration for the chemotherapies were sourced from the NHS Schedule Costs 2023/24, as presented in Table 59.[170] Combined chemotherapies administered on the same day were assumed to incur only a single drug administration cost.

The dosing regimen for each chemotherapy was listed in Table 74 with an average duration of 1.49 months assumed for each chemotherapy treatment, based on the median time duration from the Mangin *et al*. (2021) study, further validated by UK clinical experts.[84] The unit cost of each chemotherapy treatment were listed in Table 75. The treatment acquisition costs per dose (including RDI) of each chemotherapy, with and without wastage, were shown in Table 76.

Table 74: Dosing regimen of chemotherapy treatments

Treatment	Dosage regimen	Source
Dacarbazine only	850mg/m^2 on day 1 and then once every 3 weeks	Dacarbazine SmPC[136] Klee et al. (2022)[137]
Temozolomide only	200 mg/m^2 orally for 5 days every 4 weeks	Quirbt *et al*. (2007)[138]
Carboplatin only	AUC 5 mg/ml x min every 3 weeks	Casper *et al*. (1990)[139] The dosing regimen was based on clinical expert opinion[129]
Carboplatin + Paclitaxel	**Carboplatin:** -Cycle 1-4: AUC 5 mg/ml x min on day 1 of each 21-day cycle -Cycle 5-10: AUC 5 mg/ml x min on day 1 of each 21-day cycle	Flaherty *et al*. (2012)[140] The dosing regimen was based on clinical expert opinion[129]
	Paclitaxel: -125mg/m^2 on day 1 of each 21-day cycle	
Dacarbazine + Cisplatin	**Dacarbazine:** -350 mg/m^2/day on day 1 every 21-day cycle for 4 cycles	Murren *et al*.(1991)[141] The dosing regimen was based on clinical expert opinion[129]
	Cisplatin: -50 mg/m^2/day on day 1 every 21-day cycle for 4 days	

Abbreviations: AUC, Area under the curve; m, Metre; mg, Milligram; SmPC, Summary of Product Characteristics.

Table 75: Unit costs of chemotherapy regimen

Treatment	Dosage strength (mg)	Pack size/vial volume	Administration route	Cost per pack (£)	Source
Dacarbazine	100.00 200.00 500.00 1000.00	10 10 1 1	IV	59.69 107.11 27.32 57.20	eMIT 2024[168]
Temozolomide	5.00 20.00 100.00 140.00 180.00 250.00	5 5 5 5 5 5	Oral	2.01 5.49 20.03 34.29 34.44 19.74	eMIT 2024[168]
Carboplatin	50.00 150.00 450.00 600.00	1 1 1 1	IV	6.71 12.18 23.18 38.93	eMIT 2024[168]
Paclitaxel	30.00 100.00 150.00 300.00	1 1 1 1	IV	4.79 12.89 22.37 31.89	eMIT 2024[168]
Cisplatin	10.00 50.00 100.00	1 1 1	IV	3.67 19.69 37.34	eMIT 2024[168]

Abbreviations: BNF, British National Formulary; eMIT, Electronic Market Information Tool; IV,Intravenous; mg, Milligram.

Table 76: Acquisition cost of chemotherapy regimen

Treatment regimen	Drug	Treatment cycles	Dose per administration (mg)	Administration per treatment cycle	RDI (%)	Cost per cycle (£) – no wastage	Cost per cycle (£) – wastage **	Total number of cycles§	Source (RDI)
Dacarbazine only	Dacarbazine	Cycles 1-12	1,664.43	1	96.00	85.57	92.79	2.16	FDA (2011)[176]
Temozolomide only	Temozolomide	All cycles	391.63	5	99.00	30.61	51.21	1.62	Gogas *et al*. (2006)[177]
Carboplatin only	Carboplatin	All cycles	579.37	1	100.00	29.84	35.36	2.16	Lee *et al.* (2015)[178]
Carboplatin + Paclitaxel	Carboplatin	Cycles 1-4	579.37	1	100.00*	29.84	35.36	2.16	Lee *et al.* (2015)[178]
	Carboplatin	Cycle 5-10	579.37	1		29.84	35.36	0.00	Lee *et al*. (2015)[178]
	Paclitaxel	All cycles	244.77	1		26.02	35.26	2.16	Lee *et al*. (2015)[178]
Dacarbazine + Cisplatin	Dacarbazine	Cycles 1-4	685.35	1	100.00Ŧ	36.70	40.27	2.16	FDA (2011)[176]
	Cisplatin	Cycles 1-4	97.91	1		35.93	38.60	2.16	FDA (2011)[176]

Abbreviations: FDA, Food and Drug Administration; mg, Milligram; MoM, Method of moments; RDI, Relative dose intensity.
§Median time duration from Mangin et al.(2021) was assumed for all chemotherapies, at 1.49 months.
*RDI for carboplatin+paclitaxel was assumed to be the same as carboplatin only due to the absence of data.
ŦRDI for dacarbazine+cisplatin was assumed to be the same as dacarbazine only due to the absence of data.
**Note: The cost of wastage per cycle was calculated using the MoM to estimate the number of vials required in the base case, assuming no vial sharing occurs. MoM was not used for calculating wastage for carboplatin and paclitaxel.

3.5.1.5 BSC treatment cost

No acquisition or administration cost was assumed for BSC.

3.5.2 Health-state unit costs and resource use

Healthcare resource use frequency was based on NICE TA400 which assessed nivolumab in combination with ipilimumab for treating advanced (unresectable or metastatic) melanoma.[73] The health state resource use is split by health states (PF and PD) and assumes the same resource use across lifileucel and all comparators. Resource use for monitoring and disease management in the PF and PD health states was presented in Table 77. Unit costs for resource use were sourced from the NHS reference costs 2023/24 and the PSSRU 2023 based on the setting of care (Table 77). Where unit costs were not available for the current cost year, they were inflated to 2022/2023 using the latest PSSRU NHSCII pay and prices inflation index, and the HCHS pay and prices index before 2014/15 as shown in Table 78.[170,179,180] These unit costs were multiplied by resource use estimates sourced from NICE TA400 to derive per-cycle costs and one-off costs upon progression and death.[170,179,180]

In the model, patients in the C-144-01 trial who achieved long-term survival after a defined timepoint were assumed to no longer incur monitoring costs. Similarly, patients in the ipilimumab treatment who remained in the PF health state beyond the defined timepoint were also assumed to no longer require monitoring. The timepoint of 3 years was used in the base case, 5 years was used in scenario analysis.

Table 77: Unit costs and resource use per patient

Resource	Unit cost inflated to 2023/24 (£)	Health state	Resource use per cycle (per week) *				Source (unit cost)
			Lifileucel	BSC	Chemotherapy	Ipilimumab	
Oncologist visit – outpatient	188.00	PF	0.35	0.35	0.35	0.35	NHS reference costs 2023/24 Medical Oncology (Total OPATT service code 370).[170]
		PD	0.13	0.13	0.13	0.13	
Radiation oncologist visit-outpatient	139.00	PF	0.01	0.01	0.01	0.01	NHS reference costs 2023/24 Clinical Oncology Previously Radiotherapy (Total OPATT service code 800).[170]
		PD	0.02	0.02	0.02	0.02	
GP visit - outpatient	38.00	PF	0.02	0.02	0.02	0.02	PSSRU 2023: pg64 without qualifications excluding direct costs.[180]
		PD	0.34	0.34	0.34	0.34	
Palliative care physician visit-outpatient	167.50	PF	0.00	0.00	0.00	0.00	PSSRU 2023: pg36 average of outpatient medical and non-medical specialist palliative care attendance (19 years and over)[179]
		PD	0.06	0.06	0.06	0.06	
Psychologist visit-outpatient	167.20	PF	0.00	0.00	0.00	0.00	PSSRU 2014: pg183 per hour of client contact. 1 hour visit assumed. (From TA400)[73]
		PD	0.02	0.02	0.02	0.02	
Plastic surgeon visit- outpatient	147.00	PF	0.01	0.01	0.01	0.01	NHS reference costs 2023/24 Plastic Surgery (Total OPATT service code 160)[170]
		PD	0.00	0.00	0.00	0.00	
Nurse visit-outpatient	57.00	PF	0.03	0.03	0.03	0.03	NHS reference costs 2023/24 District Nurse, Adult, Face to face (TOC currency code N02AF)[170]
		PD	0.00	0.00	0.00	0.00	
Oncology/general ward – inpatient	367.08	PF	0.01	0.01	0.01	0.01	NHS reference costs 2023/24 Weighted average of excess bed days for elective and non-elective inpatients for all HRGs[170]
		PD	0.11	0.11	0.11	0.11	
Palliative care unit – inpatient	305.00	PF	0.00	0.00	0.00	0.00	PSSRU 2023: pg 36 Inpatient, specialist palliative care (19 years and over), average cost per bed day (19 years and over)[180]
		PD	0.23	0.23	0.23	0.23	
	92.00	PF	0.00	0.00	0.00	0.00	

Palliative care physician - home care		PD	0.05	0.05	0.05	0.05	PSSRU 2023: pg36 Outpatient - non medical specialist palliative care attendance.[179]
Palliative care nurse - home care	78.67	PF	0.00	0.00	0.00	0.00	NHS reference costs 2023/24 Specialist Nursing, Palliative/Respite Care, Adult, Face to face (TOC currency code N21AF)[170]
		PD	0.20	0.20	0.20	0.20	
Home aide visits	243.00	PF	0.00	0.00	0.00	0.00	PSSRU 2023: pg36 Outpatient - medical specialist palliative care attendance (19 years and over).[179]
		PD	0.43	0.43	0.43	0.43	
CT scan	141.67	PF	0.23	0.23	0.23	0.23	NHS reference costs 2023/24. Average of total for RD20A/RD21A/RD22Z.[170]
		PD	0.01	0.01	0.01	0.01	
MRI of brain	243.33	PF	0.01	0.01	0.01	0.01	NHS reference costs 2023/24 Average of total for RD01A/RD02A/RD03Z.[170]
		PD	0.00	0.00	0.00	0.00	
Chest X-ray	202.00	PF	0.07	0.07	0.07	0.07	NHS reference costs 2023/24 Contrast Fluoroscopy Procedures with duration of less than 20 minutes RD30Z (Total HRG).[170]
		PD	0.00	0.00	0.00	0.00	
PET scan	566.00	PF	0.00	0.00	0.00	0.00	NHS reference costs 2023/24 Positron Emission Tomography, 19 years and over RN07A (Total HRG).[170]
		PD	0.00	0.00	0.00	0.00	
Bone scintigraphy	532.00	PF	0.00	0.00	0.00	0.00	NHS reference costs 2023/24 Nuclear Bone Scan of two or three phases, 19 years and over RN15A (Total HRG).[170]
		PD	0.00	0.00	0.00	0.00	
Echography	159.00	PF	0.01	0.01	0.01	0.01	NHS reference costs 2023/24 Weighted average of total for RD23Z/RD24Z/RD25Z/RD26Z/RD27Z.[170]
		PD	0.00	0.00	0.00	0.00	
Complete blood count	3.00	PF	0.30	0.30	0.30	0.30	NHS reference costs 2023/24 Haematology (TOC currency code DAPS05)[170]
		PD	0.00	0.00	0.00	0.00	
Complete metabolic panel	2.00	PF	0.28	0.28	0.28	0.28	NHS reference costs 2023/24 Haematology (TOC currency code DAPS04)[170]
		PD	0.00	0.00	0.00	0.00	
	2.00	PF	0.28	0.28	0.28	0.28	

Lactate dehydrogenase		PD	0.00	0.00	0.00	0.00	NHS reference costs 2023/24 Haematology (TOC currency code DAPS04)[170]
Pain management	211.48	PF	0.00	0.00	0.00	0.00	Total pain control management unit costs from TA400.[73]
		PD	0.39	0.39	0.39	0.39	
Total cost (£)		**PF**	**121.16**	**121.16**	**121.16**	**121.16**	
		PD	**387.06**	**387.06**	**387.06**	**387.06**	

Abbreviations: BSC, Best supportive care; CT, Computed tomography; GP, General practitioner; HRG, Healthcare resource group; MRI, Magnetic resonance imagining; PD, Progressed disease; PET, Positron emission tomography; PF, Progression-free.
*Source for resource use was derived from NICE TA400.

Table 78: Inflation indices

Year	Index	Multiplier to 2022/2023	Source
2003/2004	224.8	1.58	PSSRU 2022[179]
2004/2005	232.3	1.53	
2005/2006	240.9	1.47	
2006/2007	249.8	1.42	
2007/2008	257	1.38	
2008/2009	267	1.33	
2009/2010	268.6	1.32	
2010/2011	276.7	1.28	
2011/2012	282.5	1.26	
2012/2013	287.3	1.24	
2013/2014	290.5	1.22	
2014/2015	293.1	1.21	
2015/2016	294.27	1.21	PSSRU 2023[180]
2016/2017	300.42	1.18	
2017/2018	304.15	1.17	
2018/2019	309.01	1.15	
2019/2020	315.63	1.13	
2020/2021	323.49	1.10	
2021/2022	331.80	1.07	
2022/2023	355.13	1.00	

*Costs before 2014/2025 were inflated to 2014/2015 using the HCHS index and then inflated to 2021/2022 costs using the NHSCII index. Only cost of pyrexia were before 2014/2015 (i.e. from 2013 year)
Abbreviations: HCHS, Hospital and Community Health Services; NHSCII, National Health Service Cost Inflation Index; PSSRU, Personal Social Services Research Unit.

3.5.2.1 End of life costs

End-of-life cost was applied as a one-off cost to patients upon entry into the death health state. The end-of-life cost was calculated based on the average cost derived from the Round *et al.* (2015) modelling study, which estimated the cost of cancer care during the final phases of life.[181] The Round *et al*. (2015) end-of-life cost was also used in other NICE TAs; TA429, TA561, TA627, TA689 and TA1001.[182–186]

In the model, the average health and social care costs from Round *et al*. (2015) were used in the base case and inflated to 2023/2024 costs using inflation indices from the PSSRU (as shown in Table 78).[179,180] This resulted in a cost of £7,428.05 per patient upon death.[179,180]

3.5.3 Adverse reaction unit costs and resource use

As described in 3.3.3, the model accounts for the impact of adverse events for grade 3 or above observed in 5% or more patients in any treatment arm. The unit costs associated with the management of AEs were sourced from the NHS reference costs 2023/24 and previous technology appraisals (Table 79:).[170] Where unit costs were not available for the current cost year, they were inflated to 2023/24 using the pay and prices inflation index, as shown in Table 78. The aggregate AE-related cost was applied as a one-off cost in the PF health state in the first cycle for all treatment arms, based on the assumption that AEs occurred and resolved within the first cycle of treatments. This approach was also adopted for simplicity, as the timing of AEs was not explicitly modelled due to limited data availability. This one-off application also aligns with the methodology outlined in NICE TA950 (as reflected in the company's alternative modelling following the EAG's comments).[115]

Table 79: AE management costs

Adverse event	Unit cost (£)	Source	Comment
Thrombocytopenia	346.38	NHS reference costs 2023/24[170], TA893[119]	Weighted average of DC thrombocytopenia SA12G-K.
Anaemia	392.70	NHS reference costs 2023/24[170], TA893[119]	Weighted average of Day Case Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia (SA01G– SA01K), Haemolytic Anaemia (SA03G–SA03H), Iron Deficiency Anaemia (SA04G–SA04L) and Megaloblastic Anaemia (SA05G–SA05J)
Neutropenia	388.39	NHS reference costs 2023/24[170], TA893[119]	Weighted average of DC Agranulocytosis (SA35A–E)
Lymphopenia	411.53	NHS reference costs 2023/24[170], TA893[119]	Weighted average of DC - Other haematological or Splenic disorders (SA08G-J)
Leukopenia	411.53	NHS reference costs 2023/24[170], TA893[119]	Weighted average of DC - Other haematological or Splenic disorders (SA08G-J)
Febrile neutropenia	2,058.10	NHS reference costs 2023/24[170], TA893[119]	Weighted average of NEL & NES - Other haematological or Splenic disorders (SA08G-J)
Hypophosphatemia	459.29	NHS reference costs 2023/24[170], TA893[119]	Weighted average of the codes: KC05G, KC05H, KC05J, KC05K, KC05L, KC05M, KC05N for Fluid or Electrolyte Disorders, without Interventions
Hypoxia	483.45	NHS reference costs 2023/24[170], TA893[119]	Weighted average of DC - Respiratory Failure with single

			and multiple without Interventions, with CC Score 0-11+ DZ27N-U
Hypotension	411.53	NHS reference costs 2023/24[170], TA893[119]	Weighted average of DC - Other haematological or Splenic disorders (SA08G-J)
Pyrexia	4,262.89	TA366[71], PSSRU[179,180]	Weighted average of DC Fever of Unknown origin with and without intervention WJ07B-C. Inflated from 2013/14 as codes not found in the latest NHS reference costs 2023/24.
Hypertension	361.00	NHS reference costs 2023/24[170], TA893[119]	Hypertension, Day case, EB04Z
Rash maculo-papular	462.78	NHS reference costs 2023/24[170], TA893[119]	Weighted average of DC Skin Disorders without Interventions, with CC Score 0-1-19+ JD07E-K
Chills	3,487.13	NHS reference costs 2023/24[170],	Weighted average of DC Fever of Unknown origin with and without intervention WJ07B-C. Pyrexia used as proxy.
Diarrhoea or colitis*	5,162.07	NHS reference costs 2023/24[170], TA950[115], UK KOL feedback[129]	Non-elective short stay plus infliximab plus endoscopy plus vedolizumab (see section below).
Increased alanine aminotransferase or aspartate aminotransferase	412.84	NHS reference costs 2023/24[170], TA950[115]	Non-elective short-stay, weighted average of [SA08H-J], Other Haematological or Splenic Disorders, with CC Score 0-6+
Hypophysitis	573.97	NHS reference costs 2023/24[170], TA319[74], Lorigan et al. (2014)[187]	Oxford Outcomes data reported in TA319 (endocrine disorders), inflated to 2024 GBP. Endocrine disorders were used as a proxy, as hypophysitis is a type of endocrine disorder.

*The unit cost of diarrhoa/colitis also accounts for the proportion of patients on infliximab, vedolizumab, endoscopy and its related costs.
Abbreviations: AE, Adverse event; DC, Day case; NEL, Non-elective inpatient long-stay; NES, Non-elective inpatient short-stay; NHS, National Health Service.

Diarrhoea or colitis

Immune-related gastrointestinal reactions such as diarrhoea and colitis are generally considered short-term adverse events associated with treatment using immune checkpoint inhibitors (ICIs) such as ipilimumab. However, in some cases, these events can lead to long-term complications, particularly in patients experiencing grade 3 or higher diarrhoea/colitis, which requires permanent discontinuation of ICIs such as ipilimumab.[74,188] Therefore the long term costs of diarrhoea and colitis were estimated

and applied to all treatments where these AEs occurred (lifileucel – 1.3% of patients, ipilimumab – 20% of patients).

Grade 3 or above ICI-induced diarrhoea/colitis is typically managed with symptomatic therapies such as corticosteroids, as outlined in the guidance from the East of England NHS Advisory Committee.[188] Patients who do not respond to corticosteroid are considered corticosteroid-refractory and may require infliximab as a second-line treatment. The guidance recommends considering a single dose of infliximab (5 mg/kg) for patients with corticosteroid-refractory grade 3–4 diarrhoea or colitis associated with ICIs. Some patients may require a second dose at two weeks, and in rare cases, a third dose may be necessary.[188]

Based on UK clinical expert estimates it was assumed patients with grade 3 or above diarrhoea/colitis would require:[129]

- At least five days of hospitalisation, including 4-5 days of high-dose steroids and necessary scans. The daily hospitalisation costs were sourced from the NHS 2023/24 reference costs using the codes FD10A-M (Table 80). Five days were assumed as a duration of hospitalisation. It was assumed that cost of steroids and scans will be covered by hospitalisation costs.

- Approximately 20% of patients would become corticosteroid-refractory and would require infliximab, with up to three doses needed. Based on clinical expert opinion an average of 1.5 doses of 5mg/kg of infliximab was assumed. Unit costs of infliximab and dosing is presented in Table 82. Cost of its administration is presented in Table 83.

Additionally, around 30% of patients receiving infliximab would require an endoscopy, and the majority of these patients would subsequently need treatment with vedolizumab.[129] Unit costs of vedolizumab and dosing is presented in Table 82 and

- Table 83. Cost of its administration is presented in Table 84. Unit cost of endoscopy is based on the weighted average of FE01Z – FE50A (total cost of HRGs related to endoscopy and gastrointestinal system) as shown in Table 85.

Total costs of management of grade 3 and above diarrhoea/colitis (£5,164.79) was calculated as a sum of hospital stay, cost of infliximab multiplied by a proportion of patients who are corticosteroid-refractory, cost of endoscopy and vedolizumab multiplied by a proportion of patients with infliximab who required further treatment.

Table 80: Inpatient cost for diarrhoea/colitis including management with corticosteroids

Adverse event	Inpatient length of stay (days)	Source of length of stay	Administration cost (£)	Source of administration cost	Total inpatient cost per patient (£)
Diarrhoea/colitis	5	Clinical expert opinion	566.83	NHS reference costs 2023/24[170], TA950[115], Non-elective short stay, weighted average [FD10A-M], Non-Malignant Gastrointestinal Tract Disorders with Multiple Interventions, with Single Intervention and without Intervention with CC Score 0-8+	2,834.15

Abbreviations: NHS, National Health Service.

Table 81: Proportion of patients on infliximab, vedolizumab and endoscopy

Treatment	Proportion of patients	Source
Infliximab	20%	Based on UK KOL feedback that approximately 20% of patients with diarrhoea/colitis grade 3+ will require treatment with infliximab.[129]
Vedolizumab	30% of patients receiving infliximab	Based on UK KOL feedback that approximately 30% of patients receiving infliximab would require endoscopy.[129]
Endoscopy	80% of patients receiving infliximab	Based on UK KOL feedback that majority of patients receiving infliximab would require further treatment with vedolizumab.[129]

Abbreviations: KOL, Key opinion leader. Abbrevia

Table 82: Unit cost of infliximab and vedolizumab

Treatment	Dosage strength	Pack size	Administration route	Cost per pack (£)	Source
Infliximab	100mg	1	IV	377.00	BNF2025[189]
Vedolizumab	300mg	1	IV	2,050.00	BNF2025[189]

Abbreviations: BNF, British National Formulary; IV, Intravenous; mg, milligram.

Table 83: Acquisition cost of infliximab and vedolizumab

Treatment	Dose	Treatment regimen	Acquisition cost per patient per regimen (£)*	Source	Notes
Infliximab	5mg/kg	1.5 dose	2,289.23	Infliximab SmPC[190] UK clinical expert opinion[129]	UK clinical experts recommend that patients receive up to 3 doses. As a conservative estimate, an average of 1.5 doses was assumed.[129]
Vedolizumab	300mg	4 doses	8,200.00	Vedolizumab SmPC[191] UK clinical expert opinion[129]	Based on UK KOL feedback that patients receive approximately 1–2 cycles, a conservative estimate of four doses was assumed—considering the induction phase (weeks 0, 2, and 6) as Cycle 1, followed by the first maintenance dose at week 14 as Cycle 2.[129]

*No wastage is assumed as a conservative approach.
Abbreviations: kg, kilogram; KOL, Key opinion leader; mg, milligram; SmPC, Summary of product characteristics.

Table 84: Inpatient costs for infliximab and vedolizumab

Treatment	Inpatient length of stay (days)	Source of length of stay	Administration cost (£)	Source of administration cost	Total inpatient cost per patient (£)
Infliximab	1.5	Length of stay assumed to be similar to treatment regimen	535.33	Reference codes JD07A-JD07K, weighted day case cost. National Schedule of NHS Costs - Year 2023/24[170]	802.99
Vedolizumab	4.0	Length of stay assumed to be similar to treatment regimen	535.33	Reference codes JD07A-JD07K, weighted day case cost. National Schedule of NHS Costs - Year 2023/24[170]	2,141.31

Abbreviations: NHS, National Health Service.

Table 85: Endoscopy unit cost

Treatment	Unit cost (£)	Source	Comment

Endoscopy	914.54	NHS reference costs 2023/24[170]	Weighted average FE01Z - FE50B (total cost of HRGs related to endoscopy and gastrointestinal system)

Abbreviations: HRG, Healthcare Resource Group; NHS, National Health Service.

Total costs of AE management

The AE management costs per patient were calculated based on the incidence rates (Table 54) and the respective unit costs as presented in Table 79. Table 79: The AE incidence rates for lifileucel were sourced from C-144-01 trial, ipilimumab from Da Silva *et al*. (2021) and chemotherapy from Mangin *et al*. (2021).[84,86,131] The aggregate of AE management costs calculated for each treatment in the model were shown in Table 86.

Table 86: Total adverse events management cost per patient

Treatment	Total cost (£)
Lifileucel	2,688.89
BSC	0.00
Chemotherapy	553.19
Ipilimumab	1,110.29

Abbreviations: BSC, Best supportive care.

3.5.4 Miscellaneous unit costs and resource use

No additional costs or resource use items were included in the model that have not already been listed above.

3.6 Disease Severity

The severity of the disease is "defined as the future health lost by people living with the condition with standard care in the NHS (including use of other available treatments, diagnostics, or best supportive care)" which reflects "the extent of unmet health need".[123] The “standard of care in the NHS” for this patient population comprises ipilimumab, chemotherapy and BSC, and therefore the disease severity analysis must assess these options in order to meet the definition above for the “people living with this condition”.[192] To assess severity of the disease the absolute and proportional QALY shortfall with the disease population relative to the general population with the same baseline age and gender distribution were considered. QALY shortfall is defined as the difference between the number of QALYs patients would expect to experience over the remainder of their lives with current care, compared to

the general population of the same age and sex. Absolute shortfall shows this as the number of QALYs lost while proportional shortfall shows the ratio of QALYs lost compared to the total QALYs expected. A weight is applied to the incremental QALY of the intervention based on the criteria it meets for severity weighting (i.e. 1, 1.2 or 1.7). The result of the shortfall for the intervention that provides the highest weight (for each standard of care comparator) is the one that should be used. Outside of the severity analysis, there are indicators showing high unmet need in this patient population – including that the majority patients are treated with BSC, and the lack of effectiveness of approved treatments for this patient population.

The analysis undertaken in this section provides details on the severity analysis of this patient population when treated with the NHS standard of care (ipilimumab, chemotherapy and BSC) individually by each treatment and collectively.

The starting age and sex distribution, taken from the C-144-01 trial and aligned with the model base case, is reported in Table 87. The remaining life expectancy and QoL of adult patients with previously treated unresectable or metastatic melanoma under current care was compared with that of an age- and sex-adjusted general population in line with the NICE reference case. This was assessed using the excel version of the QALY shortfall calculator by Wailoo and Tappenden (2021)[193] that was integrated into the model. The life expectancy for the general population used in the version adapted by the company was based on the latest ONS UK life tables (2020-2022)[148], and quality-adjusted using EQ-5D UK population norm values as reported by Hernández Alava *et al*. (2022)[158]. The half-cycle correction was not included as it is not applicable to the model given the model used weekly cycle lengths (as explained in Section 3.2.2.4). An annual discount rate of 3.5% was applied.[194]

The results of the QALY shortfall calculator are presented in Table 87. Total QALYs of melanoma patients receiving each standard of care treatment, which were calculated from the base case analysis, represent the benchmark QALYs. The results demonstrate lifileucel meeting the criteria for a 1.7 disease severity modifier versus chemotherapy and BSC, and a 1.2 disease severity modifier versus ipilimumab according to the proportional QALY shortfall. The absolute shortfall results were presented for completeness, demonstrating lifileucel meeting the criteria for a 1.2

disease severity modifier for ipilimumab, chemotherapy and BSC, however the proportional shortfall results provided the highest weight and were therefore used in the submission. The QALY shortfall results from the online version of the QALY shortfall calculator by Schneider *et al*. (2021)[195] were in line with version adapted by the company (presented in Table 88 and Table 89).

Table 87: Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Proportion of males	[redacted]	Section 2.3
Starting age	[redacted]	

Abbreviations: QALY, Quality-adjusted life year.

Table 88: Summary of QALY shortfall analysis, adapted by the company

Treatment	Expected total QALYs for the general population	Total QALYs of melanoma patients receiving SoC	Absolute QALY shortfall	Proportional QALY shortfall	Disease severity modifier versus comparator
Ipilimumab	14.28	0.88	13.40	93.9%	x1.2
Chemotherapy		0.56	13.72	96.0%	x1.7
BSC		0.29	13.98	98.0%	x1.7

Abbreviations: BSC, Best supportive care; QALY, Quality-adjusted life year; SoC, Standard of care.

Table 89: Summary of QALY shortfall analysis

Treatment	Expected total QALYs for the general population	Total QALYs of melanoma patients receiving SoC	Absolute QALY shortfall	Proportional QALY shortfall	Disease severity modifier versus comparator
Ipilimumab	14.39	0.90	13.51	93.9%	x1.2
Chemotherapy		0.56	13.83	96.1%	x1.7
BSC		0.29	14.10	98.0%	x1.7

Abbreviations: BSC, Best supportive care; QALY, Quality-adjusted life year; SoC, Standard of care.
Source: Schneider *et al*. (2021)[195]

Table 90: Disease severity modifiers according to absolute and proportional QALY shortfalls

Severity multiplier	Absolute QALY shortfall thresholds	Proportional QALY shortfall thresholds
x1.0	≤12	≤85%
x1.2	>12 and <18	>85% and <95%

x1.7	≥18	≥95%

Abbreviations: QALY, Quality-adjusted life year.
Source: NICE DSU TSD 23[192]

Although ipilimumab does not reach the ≥95% threshold for a 1.7 disease severity modifier, the proportional QALY shortfall is remarkably close at a value of 93.9%. When taken into account with estimates of current UK clinical practice (Table 91), ipilimumab treatment is only used for a subset of patients ([redacted]), with the majority of patients being treated with BSC ([redacted]) and chemotherapy ([redacted]), which had a proportional QALY shortfall of 98.0% and 96.1% respectively. The results of the QALY shortfall calculator adapted by the company when accounting for market share demonstrate lifileucel meet the criteria for a 1.7 disease severity modifier against all comparators according to the proportional QALY shortfall.

Table 91: Summary of QALY shortfall analysis including market share, adapted by the company

Treatment	Expected total QALYs for the general population	Total QALYs of melanoma patients receiving SoC	Market share	Absolute QALY shortfall	Proportional QALY shortfall	Disease severity modifier versus comparator
Ipilimumab	14.28	0.90	[redacted]	13.82	96.8%	x1.7
Chemotherapy		0.56	[redacted]			
BSC		0.29	[redacted]			

Abbreviations: BSC, Best supportive care; QALY, Quality-adjusted life year; SoC, Standard of care.

NICE's previous approach, the end-of-life criteria, where the cost-effectiveness threshold was adjusted to account for treatments that extend the life expectancy of patients with short life expectancy had three criteria[196]:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.
- The treatment is licensed or otherwise indicated, for small patient populations.

As mentioned in Section 3.2.2.9, patient's life expectancy with currently available treatments will likely be less than one year after disease progression.[84,87,90,131,132,84,87,90,131,132] The median survival of 8.80 months for ipilimumab and 6.03 months for chemotherapy was reported.[37,39] The mean survival (derived from calculating the area under the best fitting curve using base case assumptions) was 15.9 months for ipilimumab, 9.5 months for chemotherapy and 4.9 for BSC. TA268[77] (ipilimumab for previously treated unresectable or metastatic melanoma, 2012) and TA269[68] (vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma, 2015) are examples of previous melanoma TAs where the end-of-life criteria was met. This indicates previously treated advanced melanoma reflects a relatively small patient population with short life expectancy with the prior standard of care treatments. Therefore, lifileucel would have been eligible for the end-of-life criteria and receive an adjusted cost-effectiveness threshold of £50,000/QALY (akin to the 1.7 disease severity modifier).

Njoroge *et al*. (2024)[197] analysed 132 TAs that previously qualified for end-of-life criteria and derived disease severity modifier for each of them. A vast majority of indications previously qualifying for the end-of-life criteria would not meet the 1.7 disease severity modifier and instead receive an implied willingness-to-pay threshold of ≤£36,000/QALY. Similar conclusions were found in Batteson *et al.* (2023)[198] where out of the 20 oncology appraisals that had met the end-of-life criteria, only three would meet the 1.7 disease severity modifier. The Association of the British Pharmaceutical Industry (ABPI) reported that in NICE's retrospective analysis of 364 decisions qualifying candidate treatments or technologies for end-of-life criteria, across all corresponding appraisals the average weightings per QALY was 1.125 under the former end-of-life criteria which drops to 1.119 when using the disease severity modifier.[199]

Shield *et al*. (2023)[200] assessed 22 diseases and six disease subpopulations for potential disease severity modifier weights and found that melanoma did not receive any severity weighting despite the precedence set for melanoma achieving end-of-life criteria. In the 'task and finish group report' for the NICE manual 2022, NICE acknowledged that advanced melanoma would not receive a severity weighting

despite the precedence set for melanoma achieving an end-of-life criteria (TA268[77], TA269) stating "*The main reason why these conditions, such as advanced melanoma, would not receive a severity weighting is that although people's life expectancy may be less than two years with the relevant comparator, QoL can remain good for most of that period*." [201,202] EOL criteria did not contain a QoL element; per the 'task and finish group report' it is acknowledged that melanoma will be directly disadvantaged by the change in criteria. Given QoL is a more subjective measure than the EOL criteria, the severity modifier has more subjectivity. Further, NICE in the consultation for reviewing methods for health technology evaluation in 2020 acknowledged that there is limited evidence for introducing a specific modifier for treatments with curative potential.[203]

Based on the analysis above, the company believes 1.7 disease severity modifier is the most appropriate based on the definition, and which also reflects the high unmet need of this patient population. That best supportive care is the most common option for these patients is, in itself, reflective of the high unmet need for this population, and patients addressed by BSC show a high proportional shortfall of 98.0%. Chemotherapy also demonstrates a proportional shortfall of 96.0%. Ipilimumab is only eligible for a subset of patients, and the proportional shortfall, while <95%, is still substantial for treated patients at 93.9%. Furthermore, the QALY for ipilimumab can be viewed as optimistic given it includes the conservative assumption for long-term survival of ipilimumab patients (detailed further in Section 3.3.1.5). Additionally, the various studies mentioned above support an equality argument of lifileucel (and melanoma patients) being disadvantaged by the paradigm shift from end-of-life modifier to the severity modifier.

The severity analysis considered holistically for the "patients living with this condition" based on the "NHS standard of care" demonstrates an overall proportional shortfall of >95% and high unmet need, and therefore the 1.7 disease severity modifier.

3.7 Uncertainty

There is a lack of randomised studies comparing lifileucel with the identified relevant comparators leading to uncertainty in the clinical inputs informing the economic model.

To estimate the relative efficacy of these treatments, unadjusted analysis and STC were conducted and discussed in Section 2.10 and Section 3.3.1.

The key areas of uncertainty in the economic analysis are considered to be the following:

- Whilst mature survival data for lifileucel are available, there is a need to estimate clinical outcomes over a lifetime horizon, utilising the 4-year follow-up of the C-144-01 trial. Four-year data while substantial, represents a small proportion of a patient's further lifetime and therefore extrapolation may introduce uncertainty. This uncertainty has been addressed through the validation of the extrapolation approaches, outcomes and base case survival distribution choices with UK KOLs at an advisory board (17th October 2024) and in 1:1 meetings[16,129] Additionally, scenario analyses were performed to reflect alternative approaches and survival distributions.

- Limited survival data are available for ipilimumab and chemotherapy. Based on the SLR and review of the identified papers, only one ipilimumab study (da Silva *et al.* [2021][88]) and one chemotherapy study (Mangin *et al.* [2021][84]) were considered relevant for the inclusion in the ITC versus lifileucel and further in the cost effectiveness model. Duration of follow-up in these trials were relatively short for ipilimumab (22.1 months) and chemotherapy (the mortality events were only reported up to 12 months). These data were extrapolated over a lifetime horizon which introduced uncertainty. Outcomes and base case survival distribution choices were validated with UK KOLs at an advisory board (17th October 2024) and in 1:1 meetings.[16,129] Distribution for ipilimumab were adjusted based on their feedback. Additionally, scenario analyses were performed to reflect alternative approaches and survival distributions.

- No survival data for BSC were identified in the SLR. KOL opinion was sought to address this uncertainly. Survival on BSC was estimated based on KOL feedback that BSC patients will have 50% shorter survival compared to patients treated with chemotherapy.[16,129]

- Cohorts 2 and 4 of the C-144-01 trial have been pooled despite differences in patient characteristics (described further in Section 2.3.3). Additionally, the patients in the cohorts predominantly represented those in the United States (Table 7), introducing uncertainty of whether C-144-01 is reflective of UK clinical practice. The pooling of Cohorts 2 and 4 as well as the trial's reflectiveness of the UK was validated by UK KOLs at an advisory board (17th October 2024) for the FAS population.[16]

The uncertainty in the model is explored through extensive one-way sensitivity analyses (OWSA), probabilistic sensitivity analysis (PSA) and scenario analyses (described in Section 3.10).

3.8 Summary of base-case analysis inputs and assumptions

3.8.1 Summary of base-case analysis inputs

A summary of the key inputs used in the base case of the economic model was provided in Table 92.

Table 92: Summary of variables applied in the economic model

Variable	Value	Reference to section in submission
Model settings		
Discount rate (costs)	3.5%	3.2.2.5
Discount rate (benefits)	3.5%	3.2.2.5
Time horizon	Lifetime horizon	3.2.2.4
Cycle length	1 week	3.2.2.4
Half-cycle correction	None	3.2.2.4
Population characteristics		
Starting age (years)	[redacted]	2.3.3
Percent male	[redacted]	2.3.3
Mean weight (kg)	[redacted]	2.3.3
Efficacy		
Source of data for lifileucel versus ipilimumab	Adjusted ITC – adjusted survival based on STC results	3.3.1.2
Source of data for lifileucel versus BSC and chemotherapy	Unadjusted survival analysis – Unadjusted survival data from the clinical trials	3.3.1.2

Modelling of long-term survival	Lifileucel: MCM Ipilimumab, Chemotherapy and BSC: SPM	3.3.1.5
Cure time point for lifileucel	3 years	3.3.1.4
Cure time point for ipilimumab	3 years	3.3.1.4
Lifileucel survival distributions	PFS: Log-normal (for the uncured) OS: Exponential (for the uncured)	3.3.1.5
Ipilimumab survival distributions	PFS: Log-logistic OS: Log-normal	3.3.1.5
Survival for the cured patients	General population with SMR of 1	3.3.1.3
Chemotherapy survival distributions	PFS: Log-logistic OS: Log-normal	3.3.1.5
BSC efficacy	HR of 2 applied to chemotherapy extrapolations	3.3.1.5
Discontinuation/duration of treatment		
Lifileucel discontinuation rates	[redacted] (Patients who did receive lifileucel infusion that was in-specification of the SmPC)	Appendix K
Treatment of patients who discontinued lifileucel before getting infusion	According to estimated market shares among BSC, chemotherapy and ipilimumab	3.3.2
Ipilimumab duration	2.30 months (3.6 cycles)	3.2.3.2
Chemotherapy duration	1.49 months	3.2.3.3
Health state utilities and disutilities		
Utility for PF	0.77	3.4.5
Utility for PD	0.67	3.4.5
Disutility for lifileucel administration	0.09	3.4.6
Health state costs (per cycle)		
PF	£121.16	3.5.2
PD	£387.06	3.5.2
End of life	£7,428.05	3.5.2.1
Drug acquisition and administration costs (total costs per patient)		
Lifileucel infusion – acquisition cost	[redacted]	1.2
Lifileucel administration	[redacted]	3.5.1.2
Lifileucel pre-treatment costs		
Tumour tissue procurement	[redacted]	3.5.1.2
LD regimen	£4,686.89	3.5.1.2
Lifileucel post-treatment costs		

IL-2 including monitoring post IL-2	£6,185.15	3.5.1.2
Ipilimumab	£73,880.99	3.5.1.3
Chemotherapy	£1,311.07	3.5.1.4
BSC	£0.00	3.5.1.5
Adverse events costs (total)		
Lifileucel	£2,688.89	3.5.3
Ipilimumab	£1,110.29	3.5.3
Chemotherapy	£553.19	3.5.3
BSC	£0.00	3.5.3

Abbreviations: BSA, Body surface area; BSC, Best supportive care; HR, Hazard ratio; IL-2, Interleukin-2; ITC, Indirect treatment comparison; LD, Lymphodepletion; MCM, Mixture cure modelling; OS, Overall survival; PD, Progressed disease; PF, Progression-free; PFS, Progression-free survival; SMR, Standardised mortality ratio; SPM, Standard parametric modelling.

Assumptions

A summary of assumptions applied in the model was presented in Table 93.

Table 93: Key assumptions applied in the model

Aspect	Assumption	Justification	Source/Exploration in scenario analysis
Health state utility values	The same PF and PD utility values were applied to all interventions (lifileucel, ipilimumab, chemotherapy, BSC).	As the HRQoL data from the C-144-01 trial were unsuitable for use in the model due to limited data, utility estimates were derived from various publications and previous NICE submissions. The utility estimates for PF and PD states were calculated as averages and no differences were assumed between each individual treatment. Similar approach was used in advanced melanoma NICE appraisals, TA268, TA384, TA400 and TA410.[73,77,78,114]	A scenario analysis to explore the impact of sources with the highest and lowest PF utility values was conducted with Retel *et al.* (2018) and TA357 respectively.[70,110]
Mixture cure model for lifileucel	The model included a cure assumption for patients treated with lifileucel, where a proportion of patients would be cured at cycle 0, immediately following administration of lifileucel dose. This was determined using the mixture cure model approach, in addition to standard parametric modelling for the extrapolation of survival data. Cure assumption at time 0 is a common assumption for tractability in mixture cure modelling.	The cure assumption is supported by an observed plateau in the PFS and OS KM curves from the C-144-01 trial (DCO 30th June 2023) of the PDAwCS at approximately [redacted] and [redacted], respectively with a median follow-up of 47.4 months. The trial data are sufficiently mature to support this assumption, with endorsement from UK clinicians who have also stated that patients who remained alive without disease progression at three years and beyond are assumed cured with long-term survival similar to the general population.[16] This assumption also aligned with approaches used in CAR-Ts TAs, where a curative effect of CAR-Ts was demonstrated and extrapolated using the MCM approach.	Scenario analyses with a different cure time points (for applying general population utilities) and alternative survival distributions presented.

Long-term survival for ipilimumab	It was assumed that a percentage of patients that were PF at a defined time point (3-years) achieved long-term survival.	At the advisory board (17th October 2024), clinical experts indicated that a small proportion of patients treated with ipilimumab may achieve long-term survival.[16] In the CheckMate 067 study, investigating nivolumab, ipilimumab and their combination for previously untreated advanced melanoma, the 10-year follow-up data displayed a strong association between 3-year PFS rates and long-term survivorship rates.[130]	A scenario analysis with 5-years' time point was conducted.
SPM for ipilimumab adjusted	SPM was considered the most appropriate approach for modelling the survival of ipilimumab instead of MCM.	The PFS KM curve for ipilimumab (Figure 8) showed a small plateau at approximately 15 months but lasted until approximately 19 months before decreasing thereafter. The data for ipilimumab were also considered immature due to the relatively short follow-up time of 22.1 months. Therefore, the SPM was considered the most appropriate approach for modelling the survival of ipilimumab. However, it was suggested by the UK clinical experts that some ipilimumab patients experience long-term survival and this was accounted for and detailed in Section 3.3.1.2. That is why a functionality to account for patients who may be long term survivals (PF survival used as a proxy) was included in the model. In the base case a 3-year PF rate was used as a proxy for long term survival.	A scenario with 5-year PFS rate used as a proxy was conducted.
SPM for chemotherapy and BSC	SPM was considered the most appropriate approach for modelling the survival of chemotherapy and BSC instead of MCM.	A small plateau in the PFS KM curve for chemotherapy was seen from approximately nine months until end of follow-up. However, this plateau was short (approximately three months) and misleading as the mechanism of action for chemotherapy is a hindrance to cure. The OS curve for chemotherapy also exhibited	N/A

		a lack of plateau. This alongside the immature data represented by the follow-up time of just 12 months for chemotherapy, indicated that SPM was the most appropriate approach for modelling the survival of chemotherapy (and therefore BSC). The modelling approaches for treatments were validated by five UK clinical experts at an advisory board (17th October 2024).[16]	
BSC efficacy source and survival analysis	• Efficacy data from chemotherapy patients, Mangin *et al.* (2021)[84] was used as a proxy. • A HR of two was applied to chemotherapy PFS and OS distributions and used as a proxy for BSC PFS and OS distributions, respectively.	• Mangin *et al.* (2021)[84] was used as a proxy due to the lack of available data sources representing BSC. • Based on the advisory board (17th October 2024[16]), UK clinical experts agreed that BSC survival outcomes are approximately 50% worse than the chemotherapy. Therefore, a HR of two was applied to chemotherapy PFS to reflect the likely efficacy of patients receiving BSC.	N/A
Patients in the lifileucel arm who did not receive lifileucel infusion were assumed to receive standard of care	Patients in the lifileucel arm who did not receive lifileucel infusion were assumed to receive standard of care (ipilimumab, chemotherapy, BSC) based on market shares.	The market shares were based on discussions with UK clinical experts.[16]	A scenario analysis was conducted to assess the impact of assuming that patients in the lifileucel arm who did not receive lifileucel infusion received BSC only instead of standard of care based on market shares.
SMR for long-term survivals	An SMR of 1 was used in the base case.	UK clinicians stated that long term survivors of metastatic melanoma in our population of interest would be similar to a typical healthy person, emphasising a value of 1 for the SMR.[16,129]	SMR of 1.57 was used in a scenario analysis where a HR of 1.57 was applied to the background mortality rates derived from the UK lifetables.

Length of hospitalisation for post-lifileucel treatment	In the base case scenario, 10 hospitalisation days, comprising 2.0 days in the ICU and 8.0 days in a general ward were assumed for post-lifileucel treatment.	The numbers of inpatients and ICU days were informed were informed my UK clinician, who provided estimates of length of stay ranging from 5 to 12 days. Specifically, they assumed that 20% of patients would require ICU admission and 80% would be managed in a general ward.[16]	N/A

Abbreviations: BSC, Best supportive care; DCO, Data cut-off; HR, Hazard ratio; HRQoL, Health-related quality of life; ICU, Intensive care unit; KM, Kaplan-Meier; MCM, Mixture cure modelling; N/A: Not available; OS, Overall survival; PDAwCS, pooled data aligned with commercial specifications; PFS, Progression-free survival; SMR, Standardised mortality ratio; SPM, Standard parametric modelling

3.9 Base-case results

This section presents the base case results for the economic analysis comparing lifileucel to BSC, chemotherapy and ipilimumab in patients with previously treated unresectable or metastatic melanoma.

As detailed in Section 3.3.1.1, there were two key aspects considered for the survival analysis of lifileucel depending on the data available for the comparator:

- lifileucel (based on adjusted survival analysis (STC)) versus ipilimumab,
- lifileucel (based on unadjusted survival analysis from the C-144-01 trial) versus chemotherapy and versus BSC.

Base case cost-effectiveness results based on each of these approaches were presented separately in Section 3.9; lifileucel versus ipilimumab and lifileucel versus chemotherapy and versus BSC.

As discussed in Section 3.6, previously treated unresectable or metastatic melanoma satisfies the criteria for 1.7 disease severity modifier, therefore 1.7 weight was applied to the incremental QALY gains by lifileucel.

The base case results were presented using the list price for all comparators and the PAS price of £[redacted] ([redacted]) for lifileucel. The results for the list price of lifileucel (£[redacted]) are presented in Appendix P.

Base case results of lifileucel versus ipilimumab

Total costs, life years gained (LYG), quality-adjusted life years (QALYs), incremental results and the incremental cost-effectiveness ratio (ICER) for lifileucel (based on adjusted survival analysis (STC)) versus ipilimumab were presented in Table 94.

Using the PAS price for lifileucel and a disease severity modifier of 1.7, lifileucel generated an additional 6.08 QALYs at an additional cost of £[redacted] versus ipilimumab, resulting in an ICER of £[redacted] per QALY (Table 94). Disaggregated base case results were presented in Appendix H.

Table 94: Deterministic base case results of lifileucel with the PAS price versus ipilimumab using a 1.7 disease severity modifier

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (including 1.7 disease severity modifier)	ICER incremental (£/QALY)
Lifileucel	[redacted]	[redacted]	4.45	[redacted]	[redacted]	-	[redacted]
Ipilimumab	[redacted]	[redacted]	0.88	[redacted]	[redacted]	6.08	[redacted]

Abbreviations: BSC, Best supportive care; ICER, Incremental cost-effectiveness ratio; LYG, Life years gained; PAS, Patient access scheme; QALYs, Quality-adjusted life years
Note: 1.7 disease severity modifier has been applied to the incremental QALYs.

Base case results of lifileucel versus BSC and chemotherapy

Total costs, LYG, QALYs, incremental results and the ICER for lifileucel (based on unadjusted survival analysis from the C-144-01 trial), versus BSC and chemotherapy were presented in Table 95.

Using the disease severity modifier of 1.7:

- BSC: Lifileucel generated an additional 4.76 QALYs at an additional cost of £[redacted] versus BSC, resulting in an ICER of £[redacted] per QALY gained.
- Chemotherapy: Lifileucel generated an additional 4.30 QALYs at an additional cost of £[redacted] versus chemotherapy, resulting in an ICER of £[redacted] per QALY gained.

Disaggregated base case results were presented in Appendix H.

Table 95: Deterministic base case results of lifileucel with the PAS price versus BSC and chemotherapy using a 1.7 disease severity modifier

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (including 1.7 disease severity modifier)	ICER incremental (£/QALY)
Lifileucel	[redacted]	[redacted]	3.09	[redacted]	[redacted]	-	[redacted]
BSC	[redacted]	[redacted]	0.29	[redacted]	[redacted]	4.76	[redacted]
Chemotherapy	[redacted]	[redacted]	0.56	[redacted]	[redacted]	4.30	[redacted]

Abbreviations: BSC, Best supportive care; ICER, Incremental cost-effectiveness ratio; LYG, Life years gained; PAS, Patient access scheme; QALY, Quality-adjusted life years.
Note: 1.7 disease severity modifier has been applied to the incremental QALYs.

3.10 Exploring uncertainty

Since for modelling lifileucel survival were considered (Section 3.3.1.1), sensitivity and scenario analyses for the cost-effectiveness analyses based on each of these approaches were presented separately (Sections 3.10.1).

3.10.1 Probabilistic sensitivity analysis results

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA), whereby all appropriate parameters were assigned distributions and varied simultaneously. In each iteration, the model inputs were randomly drawn from the specified distributions summarised in Table 96. A total of 1,000 Monte Carlo iterations were recorded using the 1.7 disease severity modifier, to demonstrate the convergence of the ICERs. An incremental cost-effectiveness plane (ICEP) scatter plot and a cost-effectiveness acceptability curve (CEAC) were produced to graphically illustrate the level of variability and uncertainty in the results. The results of the list price for lifileucel were presented in Appendix P.

Table 96: Distribution options by model parameter for PSA

Parameter	Distribution
Age, Weight, BMI	Gamma distribution
Proportion of males	Beta distribution
HRs	Log normal distribution
PFS and OS extrapolations	Normal distribution (Cholesky decomposition)
Lifileucel – proportion receiving treatment	Dirichlet distribution

Lifileucel – proportion of patients who will accrue costs	Beta distribution
Chemotherapy – basket of treatment weighting	Dirichlet distribution
Treatment RDI	Beta distribution
Treatment acquisition costs	Fixed
Health state costs, AE costs, Treatment administration costs	Gamma distribution
Health state utilities, AE disutilities	Beta distribution

Abbreviations: AE, Adverse event, BMI, Body mass index, HR, Hazard ratio, OS, Overall survival; PFS, Progression-free survival; PSA, Probabilistic sensitivity analysis; RDI, Relative dose intensity.

PSA results of lifileucel versus ipilimumab

Total costs, QALYs, incremental results and the ICER for the PSA results of lifileucel (based on adjusted survival analysis (STC)) with the PAS price versus ipilimumab using a 1.7 disease severity modifier were presented in Table 97. Results of the 1000 Monte Carlo iterations were recorded on the ICEP in Figure 30. The mean PSA results for lifileucel versus ipilimumab were comparable to the base-case, resulting in a 3.9% difference in incremental QALYs (0.24 difference in incremental QALYs) and a [redacted]% difference in incremental costs (£[redacted] difference in incremental costs) which translated to [redacted]

CEAC of lifileucel versus ipilimumab was presented in Figure 31 and shows the percentage of simulations in which lifileucel is cost-effective over the WTP thresholds from £0-100,000 per QALY gained. At a WTP threshold of £30,000 per QALY, the probability of lifileucel being cost-effective was [redacted]%. [redacted]

Table 97: PSA results of lifileucel with the PAS price versus ipilimumab using a 1.7 disease severity modifier

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs (including 1.7 disease severity modifier)	ICER incremental (£/QALY)
Lifileucel	[redacted]	4.61	[redacted]	-	[redacted]
Ipilimumab	[redacted]	0.89	[redacted]	6.32	[redacted]

Abbreviations: ICER, Incremental cost-effectiveness ratio; LYG, Life year gained; PAS, Patient Access Scheme; PSA, Probabilistic sensitivity analysis; QALY, Quality-adjusted life year.
Note: 1.7 disease severity modifier has been applied to the incremental QALYs.

Figure 30: ICEP of lifileucel with the PAS price versus ipilimumab using a 1.7 disease severity modifier

[redacted]

Abbreviations: ICEP, Incremental cost-effectiveness plane; PAS, Patient Access Scheme; PSA, Probabilistic sensitivity analysis; QALY, Quality-adjusted life year; WTP, Willingness to pay.
Note: The WTP threshold reflects £30,000 per QALY.

Figure 31: CEAC of lifileucel with the PAS price versus ipilimumab using a 1.7 disease severity modifier

[redacted]

Abbreviations: CEAC, Cost-effectiveness acceptability curve; PAS, Patient access scheme.

PSA results of lifileucel versus BSC and chemotherapy

Total costs, QALYs, incremental results and the ICER for the PSA results of lifileucel (based on unadjusted survival analysis from the C-144-01 trial) with the PAS price versus BSC and chemotherapy using a 1.7 disease severity modifier were presented in Table 98. Results of the 1000 Monte Carlo iterations were recorded on the ICEP in Figure 32.

The mean PSA results for lifileucel versus BSC were comparable to the base-case, resulting in a 5.2% difference in incremental QALYs (0.25 difference in incremental QALYs) and a [redacted]% difference in incremental costs (£[redacted] difference in incremental costs) which translated to [redacted]The mean PSA results for lifileucel versus chemotherapy were comparable to the base-case, resulting in a 5.6% difference in incremental QALYs (0.24 difference in incremental QALYs) and a [redacted]% difference in incremental costs (£[redacted]difference in incremental costs) which translated to [redacted]

CEAC of lifileucel versus BSC and chemotherapy was presented in Figure 33 and shows the percentage difference of simulations in which lifileucel is cost-effective over the WTP thresholds from £0-100,000 per QALY gained.

Table 98: PSA results of lifileucel with the PAS price versus BSC and chemotherapy using a 1.7 disease severity modifier

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs (including 1.7 disease severity modifier)	ICER incremental (£/QALY)
Lifileucel	[redacted]	3.24	[redacted]	-	[redacted]
BSC	[redacted]	0.30	[redacted]	5.00	[redacted]
Chemotherapy	[redacted]	0.57	[redacted]	4.54	[redacted]

Abbreviations: BSC, Best supportive care; ICER, Incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALY, Quality-adjusted life year.
Note: 1.7 disease severity modifier has been applied to the incremental QALYs.

Figure 32: ICEP of lifileucel with the PAS price versus BSC and chemotherapy using a 1.7 disease severity modifier

[redacted]

Abbreviations: BSC, Best supportive care; ICEP, Incremental cost-effectiveness plane; PAS, Patient Access Scheme; PSA, Probabilistic sensitivity analysis; QALY, Quality-adjusted life year; WTP, Willingness to pay.
Note: ICEP was created for a comparison versus chemotherapy and BSC. Ipilimumab was not considered in these settings. The WTP threshold reflects £30,000 per QALY

Figure 33: CEAC of lifileucel with the PAS price versus BSC and chemotherapy using a 1.7 disease severity modifier

[redacted]

Abbreviations: BSC, Best supportive care; CEAC, Cost-effectiveness acceptability curve; PAS, Patient access scheme.
Note: CEAC was created for a comparison versus chemotherapy and BSC. Ipilimumab was not considered in these settings. The WTP threshold reflects £30,000 per QALY

3.10.2 Deterministic sensitivity analysis

One-way deterministic sensitivity analysis (OWSA) involves varying one parameter at a time to assess how sensitive the model results are to different values. The OWSA has been conducted by allocating a low value and high value to each parameter, where these values correspond to the lower and upper bounds of the 95% confidence interval (CI). In the absence of CI data, the standard error was assumed to be 20% of

the mean for all variables. The estimated standard error is used to predict the upper and lower bound of the parameters' CI. This approach allows for an understanding of how robust the model results are to changes in individual input parameters. A tornado diagram has been developed to graphically present the parameters that have the greatest effect on the results.

OWSA results of lifileucel versus ipilimumab

The top ten parameters yielding the biggest impact on cost-effectiveness results are presented in Table 99 and Figure 34 for lifileucel versus ipilimumab. The top three most sensitive parameters were PFS distribution for lifileucel, PD utility and OS distribution for lifileucel. PFS distribution for lifileucel is a particularly sensitive parameter due both to the cure rates and the covariance matrix of the distribution being varied.

Table 99: Top 10 parameters from the OWSA results of lifileucel with the PAS price versus ipilimumab using a 1.7 disease severity modifier

Parameter	Lower bound ICER (£)	Upper bound ICER (£)	Difference between upper bound and lower bound (£)
Lifileucel – PFS	[redacted]	[redacted]	[redacted]
Lifileucel - PD utility	[redacted]	[redacted]	[redacted]
Lifileucel – OS	[redacted]	[redacted]	[redacted]
Lifileucel - PF utility	[redacted]	[redacted]	[redacted]
Lifileucel PD total cost	[redacted]	[redacted]	[redacted]
Ipilimumab - PD utility	[redacted]	[redacted]	[redacted]
Ipilimumab – PFS	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]
Ipilimumab PD total cost	[redacted]	[redacted]	[redacted]
Ipilimumab – OS	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, Incremental cost-effectiveness ratio; OS, Overall survival; OWSA, One-way sensitivity analysis; PAS, Patient access scheme; PD, Progressed disease; PFS, Progression-free survival.

Figure 34: OWSA tornado diagram of lifileucel with the PAS price versus ipilimumab using a 1.7 disease severity modifier

[redacted]

Abbreviations: OS, Overall survival; OWSA, One-way sensitivity analysis; PAS, Patient access scheme; PD, Progressed disease; PF, Progression free; PFS, Progression-free survival.

OWSA results of lifileucel versus BSC and chemotherapy

The top ten parameters yielding the biggest impact on cost-effectiveness results are presented in Table 100 and Figure 35 for lifileucel versus BSC. The top three most sensitive parameters were OS distribution for lifileucel, PFS distribution for lifileucel and PD utility. OS distribution for lifileucel and PFS distribution for lifileucel are particularly sensitive parameters due to both the cure rates and the covariance matrix being varied.

Table 100: Top ten parameters from the OWSA results of lifileucel with the PAS price versus BSC using a 1.7 disease severity modifier

Parameter	Lower bound ICER (£)	Upper bound ICER (£)	Difference between upper bound and lower bound (£)
Lifileucel - OS	[redacted]	[redacted]	[redacted]
Lifileucel - PFS	[redacted]	[redacted]	[redacted]
Lifileucel - PD utility	[redacted]	[redacted]	[redacted]
Lifileucel - PF utility	[redacted]	[redacted]	[redacted]
Lifileucel PD total cost	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]
BSC - PF utility	[redacted]	[redacted]	[redacted]
Lifileucel total - Administration cost per patient per regimen (£)	[redacted]	[redacted]	[redacted]
BSC - PD utility	[redacted]	[redacted]	[redacted]
Percentage male	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, Best supportive care; ICER, Incremental cost-effectiveness ratio; OS, Overall survival; OWSA, One-way sensitivity analysis; PAS, Patient access scheme; PD, Progressed disease; PF, Progression free; PFS, Progression-free survival.

Figure 35: OWSA tornado diagram of lifileucel with the PAS price versus BSC using a 1.7 disease severity modifier

[redacted]

Abbreviations: BSC, Best supportive care; OS, Overall survival; OWSA, One-way sensitivity analysis; PAS, Patient access scheme; PD, Progressed disease; PFS, Progression-free survival

The top ten parameters yielding the biggest impact on cost-effectiveness results are presented in Table 101 and Figure 36 for lifileucel versus chemotherapy. The top three most sensitive parameters were OS distribution for lifileucel, PFS distribution for lifileucel and PD utility. PFS distribution for lifileucel and OS distribution for lifileucel are particularly sensitive parameters due to both the cure rates and the covariance matrix being varied.

Table 101: Top ten parameters from the OWSA results of lifileucel with the PAS price versus chemotherapy using a 1.7 disease severity modifier

Parameter	Lower bound ICER (£)	Upper bound ICER (£)	Difference between upper bound and lower bound (£)
Lifileucel - OS	[redacted]	[redacted]	[redacted]
Lifileucel - PFS	[redacted]	[redacted]	[redacted]
Lifileucel - PD utility	[redacted]	[redacted]	[redacted]
Chemotherapy - OS	[redacted]	[redacted]	[redacted]
Lifileucel - PF utility	[redacted]	[redacted]	[redacted]
Chemotherapy - PF utility	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]
Lifileucel PD total cost	[redacted]	[redacted]	[redacted]
Chemotherapy - PD utility	[redacted]	[redacted]	[redacted]
Lifileucel total - Administration cost per patient per regimen (£)	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, Incremental cost-effectiveness ratio; OS, Overall survival; OWSA, One-way sensitivity analysis; PAS, Patient access scheme; PD, Progressed disease; PFS, Progression-free.

Figure 36: OWSA tornado diagram of lifileucel with the PAS price versus chemotherapy using a 1.7 disease severity modifier

[redacted]

Abbreviations: OS, Overall survival; OWSA, One-way sensitivity analysis; PAS, Patient access scheme; PD, Progressed disease; PF, Progression-free; PFS, Progression-free survival.

3.10.3 Scenario analysis

Various scenario analyses were conducted to explore the impact of assumptions that were included in the base case analysis. The scenario analyses conducted in the model were presented in Table 102.

Table 102: Scenario analyses included in the model

#	Category	Base case	Scenario
		Value	Value
1	FAS discontinuation		
	Patients who died between tumour harvest and lifileucel infusion (%)	[redacted]	[redacted]
	Patients who discontinued between tumour harvest and lifileucel infusion for medical reasons[a] (%)	[redacted]	[redacted]
	Patients who received lifileucel infusion that is out-of-SmPC specification (%)	[redacted]	[redacted]
	Patients who received lifileucel infusion that met the SmPC specification (%)	[redacted]	[redacted]
2	Treatment after lifileucel discontinuation	Comparator's market share	BSC only
	BSC	[redacted]	100.0%
	Chemotherapy	[redacted]	0.0%
	Ipilimumab	[redacted]	0.0%
3	1.5% discount rates	3.50%	1.50%
4	Time to cure	3 years	5 years
5	Lifileucel PFS distribution	Lognormal MCM	Exponential MCM
6	Lifileucel PFS & OS distributions	PFS: Log-logistic MCM OS: Exponential MCM	PFS: Log-logistic MCM OS: Log-logistic MCM
7	Ipilimumab PFS	Log-logistic	Generalised Gamma
8	Ipilimumab OS	Lognormal	Log-logistic
9	Chemotherapy PFS	Log-logistic	Lognormal
10	Chemotherapy OS	Lognormal	Log-logistic
11	SMR 1.57	1.00	1.57
12	No wastage (vial sharing)	Wastage	No wastage
13	Ipilimumab treatment duration	3.6 doses	4 doses
14	Retel et al. (2018) utility	Average of all sources: PF: 0.77; PD: 0.67	PF: 0.85; PD; 0.59
15	TA357 utility*		PF: 0.74; PD; 0.69

Abbreviations: BSC, Best supportive care; Exp, Exponential; FAS, Full Analysis Set; ICER, Incremental cost-effectiveness ratio; OS, Overall survival; PFS, Progression-free survival; QALY, Quality adjusted life year; SMR, Survival Mortality Ratio.

[a]Medical reasons include adverse events, the start of a new anticancer therapy, disease progression, withdrawal from patients, withdrawals of consents and other.

*The utility values, for both PF and PD were calculated as the average of the mean utility values from MK3475 2mg and chemotherapy.

Scenario analysis of lifileucel versus ipilimumab

Table 103 present the results of thee scenario analyses for lifileucel versus ipilimumab. The scenario analysis results are predominantly stable with only the 1.5% discount rate reducing the ICER by [redacted] This discount rate supports lifileucel's high up front costs and long-term health benefits.

Table 103: Scenario analysis results of lifileucel with the PAS price versus ipilimumab using a 1.7 disease severity modifier

#	Scenario	Deterministic ICER (£/QALY)
0	Base case	[redacted]
1	FAS discontinuation	[redacted]
2	BSC only after lifileucel discontinuation	[redacted]
3	1.5% discount rates	[redacted]
4	5-year cure time point	[redacted]
5	Lifileucel exponential MCM for PFS	[redacted]
6	Lifileucel log-logistic MCM for both PFS & OS	[redacted]
7	Ipilimumab generalised gamma PFS	[redacted]
8	Ipilimumab log-logistic OS	[redacted]
9	Chemotherapy log-normal PFS	[redacted]
10	Chemotherapy log-logistic OS	[redacted]
11	SMR 1.57	[redacted]
12	No wastage (vial sharing)	[redacted]
13	Ipilimumab 4 doses	[redacted]
14	Retel et al. (2018) utility	[redacted]
15	TA357 utility	[redacted]

Abbreviations: BSC, Best supportive care; Exp, Exponential; FAS, Full Analysis Set; ICER, Incremental cost-effectiveness ratio; OS, Overall survival; PFS, Progression-free survival; QALY, Quality adjusted life year; SMR, Survival Mortality Ratio.

Scenario analysis of lifileucel versus BSC and chemotherapy

Table 104 present the results of these scenario analyses for lifileucel (based on unadjusted survival analysis from the C-144-01 trial), versus BSC and chemotherapy. The scenario analysis results are predominantly stable with only the 1.5% discount rate reducing the ICER by [redacted] This discount rates supports lifileucel's high up front costs and long-term health benefits.

Table 104: Scenario analysis results of lifileucel with the PAS price versus BSC and chemotherapy using a 1.7 disease severity modifier

#	Scenario	Deterministic ICER (£/QALY)	
		Chemotherapy	BSC
0	Base case	[redacted]	[redacted]
1	FAS discontinuation	[redacted]	[redacted]
2	BSC only after lifileucel discontinuation	[redacted]	[redacted]
3	1.5% discount rates	[redacted]	[redacted]
4	5-year cure time point	[redacted]	[redacted]
5	Lifileucel exponential PFS	[redacted]	[redacted]
6	Lifileucel log-logistic PFS & OS	[redacted]	[redacted]
7	Ipilimumab generalised gamma PFS	[redacted]	[redacted]
8	Ipilimumab log-logistic OS	[redacted]	[redacted]
9	Chemotherapy log-normal PFS	[redacted]	[redacted]
10	Chemotherapy log-logistic OS	[redacted]	[redacted]
11	SMR 1.57	[redacted]	[redacted]
12	No wastage (vial sharing)	[redacted]	[redacted]
13	Ipilimumab 4 doses	[redacted]	[redacted]
14	Retel et al. (2018) utility	[redacted]	[redacted]
15	TA357 utility	[redacted]	[redacted]

Abbreviations: BSC, Best supportive care; Exp, Exponential; FAS, Full Analysis Set; ICER, Incremental cost-effectiveness ratio; OS, Overall survival; PFS, Progression-free survival; QALY, Quality adjusted life year; SMR, Survival Mortality Ratio.Abbreviations: BSC, Best supportive care; Exp, Exponential; FAS, Full Analysis Set; ICER, Incremental cost-effectiveness ratio; OS, Overall survival; PFS, Progression-free survival; QALY, Quality adjusted life year; SMR, Survival Mortality Ratio.

3.11 Subgroup analysis

No subgroups are considered in the cost-effectiveness analysis.

3.12 Benefits not captured in the QALY calculations

Lifileucel is a potentially curative treatment with a significant proportion of patients achieving survival close to general population survival after treatment. While an attempt has been made to include this impact on patients' quality of life, the QALY estimations may not fully capture the significant positive impact and convenience of patients having a one-time treatment with curative potential.

Additionally, it is expected that lifileucel treatment will reduce carer burden from both economic and quality of life perspective, which was not included in the economic analysis. Further there is the potential that lifileucel may enable those of working age to return to work, saving productivity losses which were again not captured in the economic analysis.

These aspects, if included in the analysis, would further improve the cost-effectiveness of lifileucel.

3.13 Validation

3.13.1 Validation of cost-effectiveness analysis

During the development of the cost-effectiveness model expert input was sought to validate key aspects of the analysis. An advisory board with 5 UK KOLs (17th October 2024), followed up with 1:1 interviews were conducted with the following key areas validated:

- Current treatment pathways, place of lifileucel and eligibility in UK clinical practice,
- Generalisability of lifileucel efficacy data sources,
- Results of ITC versus ipilimumab using STC, which were further included in the cost-effectiveness analysis,
- Cost effectiveness model structure (PSM), approaches (SPM versus MCM) to survival analyses and usage of clinical data,
- Using an SMR=1 in the base case,

- Selection of base-case distributions for long-term survival extrapolations,
- Health care resource utilization and costs related to lifileucel pre-, post-infusion and infusion, comparators, health states and adverse events management.

Feedback provided during both the advisory board and 1:1 interviews was summarized in the reports provided as a reference in this submission.[16,129] This feedback was also incorporated into the cost-effectiveness model.

The cost-effectiveness model was quality assured by a senior health economist not involved in the model building process who reviewed the model for coding errors, inconsistencies, and plausibility of inputs and outputs. The model was also subject to stress testing of extreme scenarios to test for technical modelling errors and plausibility of results. All changes to the model were made by a health economist, and each change was fully quality controlled by a second health economist.

3.14 Interpretation and conclusions of economic evidence

A de novo economic model was developed to assess cost-effectiveness of lifileucel in the treatment of adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor. The patient population considered in this economic analysis is in line with the C-144-01 trial, the final scope, the decision problem and the anticipated UK licensed indication for lifileucel.[86]

As detailed in Section 3.2.2.3, the three state (progression free, progressed disease and death) PSM structure was selected for the economic analysis due to availability of relevant and mature data (i.e. availability of PFS and OS survival curves), precedence of modelling in melanoma and CAR-T TAs by NICE (nine out of the 12 melanoma TAs used PSM), along with other considerations (flexibility, avoids uncertainty caused by splitting OS data as pre and post-progression for STM structure).

In the model, lifileucel was compared to ipilimumab, chemotherapy and BSC. These treatment options reflect the most relevant comparators currently licenced and being used in UK clinical practice, as validated with UK KOLs.

Lifileucel efficacy data were obtained directly from the C-144-01 study (DCO 30th June 2023).[86] The baseline characteristics of the patient population in the C-144-01 trial were considered generalisable to the UK population who are previously treated with melanoma, as confirmed by UK clinicians.[17] Lifileucel efficacy was estimated based on the PDAwCS from Cohorts 2 and 4 were pooled and utilised as the base case of the model to maximise the sample size. Due to a curative potential of lifileucel, an MCM approach was considered and adopted in the base case to extrapolate survival outcomes over a lifetime horizon. For ipilimumab and chemotherapy, clinical data were obtained from studies identified through the SLR. BSC efficacy was estimatedby modifying survival outcomes associated with chemotherapy, as no survival data for BSC was identified in the SLR. . All survival extrapolations (selection of the best distributions and outcomes) were extensively validated with experts during an advisory board with 5 UK KOLs, followed up with 1:1 interviews.[16,129]

The UK NHS and PSS perspective was adopted in the analysis. Inputs related to resources utilization were sourced from previous TAs in melanoma, where possible. Costs inputs were obtained from eMIT, BNF, NHS reference costs 2023/24 and PSSRU 2023. Costs and resources were validated with UK clinical experts.[16,129]

Utilities were derived from previous melanoma TAs and other relevant sources identified during the SLR.

Overall, the deterministic ICER for lifileucel at the PAS price of £[redacted] versus ipilimumab using a 1.7 disease severity modifier was £[redacted] per QALY. The probabilistic mean ICER (average across all simulations) was £[redacted] per QALY with a [redacted]% probability being cost-effective at a WTP threshold of £30,000 according to the CEAC. Therefore, based on the probabilistic result, lifileucel has a high likelihood of being cost-effective for patients with unresectable or metastatic melanoma who previously treated with a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor when compared with ipilimumab.

The deterministic ICER for lifileucel at the PAS price of £[redacted] versus BSC and chemotherapy (using a 1.7 disease severity modifier) was £[redacted] per QALY and £[redacted] per QALY, respectively. Comparison of lifileucel to chemotherapy and BSC was based on unadjusted survival analysis. As the only relevant source identified to inform the chemotherapy outcomes (Mangin *et al.* [2021][84]) had substantial limitations related to the small sample size and limited patient data reported, it was deemed unfeasible to conduct a robust STC for lifileucel versus chemotherapy. Despite the inherent limitations of a naïve, unadjusted analysis versus chemotherapy, the results of this analysis were presented for transparency.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Lifileucel for previously treated unresectable or metastatic melanoma ID3863

Summary of Information for Patients (SIP)

March 2025

File name	Version	Contains confidential information	Date
ID6383_Lifileucel in unresectable melanoma	1.0	No	10 March 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Active ingredient: Lifileucel **Brand name**: (AMTAGVI®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Lifileucel is under review for the treatment of adult patients with unresectable or metastatic melanoma previously treated with a PD-1 (anti-programmed cell death protein) blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor.[1]

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The marketing authorisation for lifileucel is currently under review by the Medicines and Healthcare products Regulatory Agency (MHRA). For expected approval date, please see the NICE company submission. The MHRA regulates medicines in the UK.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

To date, no direct financial support has been provided. Planned sponsorship support for the *Melanoma Focus* conference in October, 2025 (**£8,000-12,000):** Provides an exhibit table where

we plan to raise awareness and education around our clinical trial (TILVANCE-301) amongst potential investigators and referring clinicians.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Advanced melanoma is an advanced, aggressive form of skin cancer.

Melanoma is a type of skin cancer that affects melanocytes, the cells which produce the pigment that gives skin its' colour. Melanoma is classified into various stages, depending on how deeply it has grown into the skin.[2] In more advanced and aggressive forms of melanoma (stage III and IV), the cancer cells have spread from the initial site (the primary melanoma) to other parts of the body, causing a significant and diverse symptom burden for patients. [3,4]

General symptoms of advanced stage melanoma may include hard or swollen lymph nodes, hard lumps on your skin, unexplained pain, unexplained weight loss, feeling unwell or fatigued, jaundice, and abdominal pain. Advanced melanoma, where the cancer has spread to distant parts of the body, can cause a wide range of symptoms, affecting areas such as the lungs, liver, lymph nodes, bone, and the brain.[5]

Melanoma can develop due to inherited genetic mutations, but it can also be due to specific gene mutations that happen over time. One of the most common gene mutations that leads to melanoma is called the BRAF mutation, which accounts for around 50% of all melanomas.[6,7] As this mutation is so common, it has been a major target for developing specialised cancer treatment.

Melanoma is the fifth most common cancer in the world

The number of people diagnosed with melanoma increased by 182.3% from 1990 to 2021.[8] Approximately 15% of patients are diagnosed at the advanced stage.[9]

Melanoma is an aggressive disease with a high mortality risk if not treated in a timely manner.[10,11] Melanoma deaths have increased by 86.1% from 1990 to 2021 and in the United Kingdom (UK) alone, melanoma is responsible for 2,314 deaths a year.[12,13] While patients with Stage IIIc disease have a 5-year survival rate of 69%, this reduces to just 32% for Stage IIId disease, and 22.5% for Stage IV.[14]

Despite advances in first-line treatment of advanced melanoma, most patients do not achieve long-term benefits of treatment in terms of efficacy. Survival following disease progression on first-line immune checkpoint inhibitor therapy is poor, with real-world evidence showing median overall survival (OS), measured as time from randomization or first dose of treatment until when half the patients have died and half are still alive, between 4.0 to 12.3 months in the second-line of treatment setting and beyond.[15,16] Moreover, these treatments can lead to numerous treatment-emergent adverse events (TEAEs), with over a third (65%) of patients discontinuing therapy due to TEAEs.[17]

Advanced melanoma significantly affects the quality of life (QoL) of patients
The negative QoL impact is driven by the physical burden from disease-related symptoms as well as side-effects associated with treatment such as rash, fatigue, and joint pain.[18] Patients with melanoma also suffer from depression, anxiety, and negative social impact from having to miss work/education and disruption to their normal lives, causing emotional distress.[19]

Advanced melanoma places a significant burden on families/caregivers
Macmillan Cancer Support UK estimates that around 1.5 million people are caring for someone with cancer, spending an average of 17.5 hours a week looking after them.[20] This represents a substantial burden to caregiver's quality of life, affecting them both physically and mentally. The demands of caregiving mean that 20-35% of carers experience one or more issues with their own physical health, including exhaustion, insomnia and weight gain. Furthermore, up to 70% of carers experience issues with their mental health, primarily related to disrupted schedules, financial problems and emotional stress.[21]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

The stage and risk level of melanoma are determined by disease presentation at diagnosis. Abnormal pigmented lesions are evaluated using the European Society for Medical Oncology (ESMO) guidelines, which recommends following the 'ABCD' rule. This rule checks for asymmetry (whether the shape is uneven), irregular borders, colour heterogeneity (mixed or unusual colours) and dynamics (evolution in colours, elevation or size).[22] Doctors may also conduct a magnified skin examination and full body imaging to aid diagnosis.[22]

If a skin cancer is suspected, a biopsy may be required to confirm the diagnosis of melanoma. A biopsy is a minor procedure where a small sample of the affected area is taken.[23] If advanced disease is suspected at diagnosis, a comprehensive staging protocol is initiated, including whole-body computed tomography (CT), magnetic resonance imaging (MRI) of the brain, evaluation of serum lactate dehydrogenase (LDH) levels and classification of Eastern Cooperative Oncology Group (ECOG) status are obtained, to assess the extent of disease, evaluate the presence of brain metastases and assess key clinical indicators of metastasis, respectively.[3] ECOG is a scoring system used to evaluate patient's overall health and physical functioning with the scale ranging from 0 (fully active) to 5 (death), with scores 0-2 indicating that patients are able to carry out their daily activities.[24]

For patients with advanced melanoma, determining the type of genetic mutation status is important for assessing eligibility for targeted therapy. Genetic screening is a key tool and has become standard-of-care in modern clinical management[25]. This allows clinicians to select the most suitable treatment for patients , while also guiding eligibility for clinical trials[25].

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:

- if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
- are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Current management

There are several treatment options available to patients with advanced melanoma which aim to improve QoL and prolong the survival of patients.[26] These include immunotherapy via immune checkpoint inhibitors (ICIs), targeted therapy using signal transduction inhibitors (such as BRAF or MEK inhibitors), chemotherapy, and best supportive care.[26] The use of ICIs, such as pembrolizumab and nivolumab (PD-1 blocking antibodies that target PD-1 receptor), has led to a considerable improvement in patient outcomes for Stage IIIC-IV melanoma.[27]

In the UK for the treatment of advanced melanoma are managed according to NICE melanoma assessment and management guidelines (NG14, 2022).[28] According to these guidelines, the recommended first-line treatment is nivolumab plus ipilimumab (an anti–cytotoxic T-lymphocyte antigen-4 [CTLA-4] antibody), with pembrolizumab or nivolumab monotherapy as an alternative if the combination therapy is unsuitable or unacceptable.[28]

In the event of rapid disease progression or when immunotherapy is not recommended or unsuitable, the recommended next line of treatment is largely dependent on patient's BRAF status. In such cases, targeted BRAF kinase inhibitors, such as vemurafenib and dabrafenib, are typically recommended. These inhibitors can also be used in combination with MEK inhibitors, such as trametinib and binimetinib.[28]

If patients are not eligible for nivolumab plus ipilimumab, pembrolizumab monotherapy, nivolumab monotherapy, or targeted treatment for first line of treatment, they are recommended to receive either of the following therapies, beside the possibility of entering a clinical trial:[28]

- Ipilimumab as a monotherapy,
- Chemotherapy such as dacarbazine,
- Best supportive care, which consists of symptom management, palliative care, palliative radiotherapy, and emotional and practical support,

During the course of advanced melanoma treatment, only one line of PD-1 treatment, and only one line of BRAF inhibitors (where applicable, with or without MEK inhibitors) are reimbursed by the National Health Service (NHS), meaning retreatment with these agents is not an option, thereby limiting effective treatment options that improve outcomes at second-line setting and beyond.[29]

Therefore, there is a significant unmet need for a one-time treatment offering improved efficacy and statistical cure (i.e., long-term survivorship of over three years) for patients with advanced melanoma who have progressed on currently available treatment options according to guidelines. There is also currently no curative treatment for these patients.

Introduction to lifileucel

Lifileucel is a novel tumour-infiltrating lymphocytes (TIL) cell therapy for the treatment of advanced melanoma, which has the potential to provide statistical cure for patients.
TIL are immune cells which naturally target tumours in the body. TIL cell therapies extract these cells from the patients' own tumour and grow them in a laboratory. They are then administered

back to the patient. It is proposed that lifileucel works by these immune cells recognising tumours and causing cell death of the cancerous cells.[1]

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Impact on patient QoL

Melanoma significantly impacts patients' health-related QoL. A review of 16 studies of patients affected by melanoma across Europe, Oceania and North America found that HRQoL declined as the disease progresses.[30] In early stages, melanoma is often unnoticed, with changes in mole size, shape or colour. As the disease advances, non-specific symptoms such as weight loss, tiredness, and pain may begin to surface and, after the spread of melanoma, patients start experiencing significant symptom burden that affects multiple organ systems.[5,31,32] Interviews with 29 adult Canadian patients highlighted that advanced melanoma rapidly diminishes patients' overall functioning and HRQoL.[33] progresses.[30] In early stages, melanoma is often unnoticed, with changes in mole size, shape or colour. As the disease advances, non-specific symptoms such as weight loss, tiredness, and pain may begin to surface and, after the the spread of melanoma spreads, patients start experiencing significant symptom burden that affects multiple organ systems.[5,31,32] Interviews with 29 adult Canadian patients highlighted that advanced melanoma rapidly diminishes patients' overall functioning and HRQoL.[33]

This decline in HRQoL is driven by both the symptoms of the disease and the substantial physical impact of treatments. Common treatment-related adverse effects, including rash, tiredness, and joint pain, often have a delayed onset and prolonged course, further amplifying the challenges faced by these patients.[18,34,35] This decline in HRQoL is driven by both the symptoms of the disease and the substantial physical impact of treatments. Common treatment-related adverse effects, including rash, tiredness, and joint pain, often have a delayed onset and prolonged course, further amplifying the challenges faced by these patients.[18,34,35]

Beyond physical burden, emotional and psychological wellbeing of patients with advanced melanoma are also impacted. Almost half of patients with advanced melanoma reported that they experienced an altered sense of self and were struggling with self-identity.[33] Similarly, melanoma patients reported significant higher depression and fear of disease recurrence, with an average Patient Health Questionnaire-9 (PHQ-9) score of 3.87, compared to 2.38 for the general population. The scale ranges from zero (no impact) to 4 (significant impact on daily life).[36]Beyond physical burden, emotional and psychological wellbeing of patients with advanced melanoma emotional wellbeing and psychological are also impacted. Almost half of patients with advanced melanoma reported that they experienced an altered sense of self and were struggling with self-identity.[33] Similarly, melanoma patients reported significant higher depression and fear of disease recurrence, with an average Patient Health Questionnaire-9 (PHQ-9) score of 3.87, compared to 2.38 for the general population. The scale ranges from zero (no impact) to 4 (significant impact on daily life).[36]

Impact of caregiver QoL
Furthermore, 33% of caregivers, regardless of the patient's disease stage, have reported at least one unmet need, with the most common being psychological/emotional support. Notably, 35% of caregivers sought support from a psychologist.[37] The impact on caregiver QoL is significant, mainly due to disrupted schedules, financial strain, and emotional stress,[21] regardless of the patient's disease stage.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Lifileucel has a new and novel mechanism of action to treat melanoma
Lifileucel is distinct from current therapies in the following features:

- It is a single dose, one-time treatment compared to immune checkpoint inhibitor therapies, targeted therapy, or chemotherapy which are given as courses or continuously
- It is manufactured from the patient's own immune cells and is given as part of a one-time cell therapy regimen
- It uses to the patient's own immune system to fight cancer cells
- It offers the potential of statistical cure for patients

The proposed mechanism of action of lifileucel is that it works by recognising tumours and activating other immune cells which cause the death and destruction of the cancerous cells.[38,39]The proposed mechanism of action of lifileucel is that it works by recognising tumours and activating other immune cells which cause the death and destruction of the cancerous cells.[38,39] The patient-specific, single-dose nature of lifileucel represents a notable shift in the treatment approach of this aggressive disease, offering potential statistical cure to these patients.

Overall, lifileucel represents a promising advancement in the field of oncology, offering hope for advanced melanoma patients with limited treatment options. Furthermore, trial data shows that a majority of patients who initially responded to treatment were still having a response over a year later, showing a durability of response to treatment. After four years of treatment, the median duration of response was not reached i.e. more than 50% of the trial population were still responding.[40]

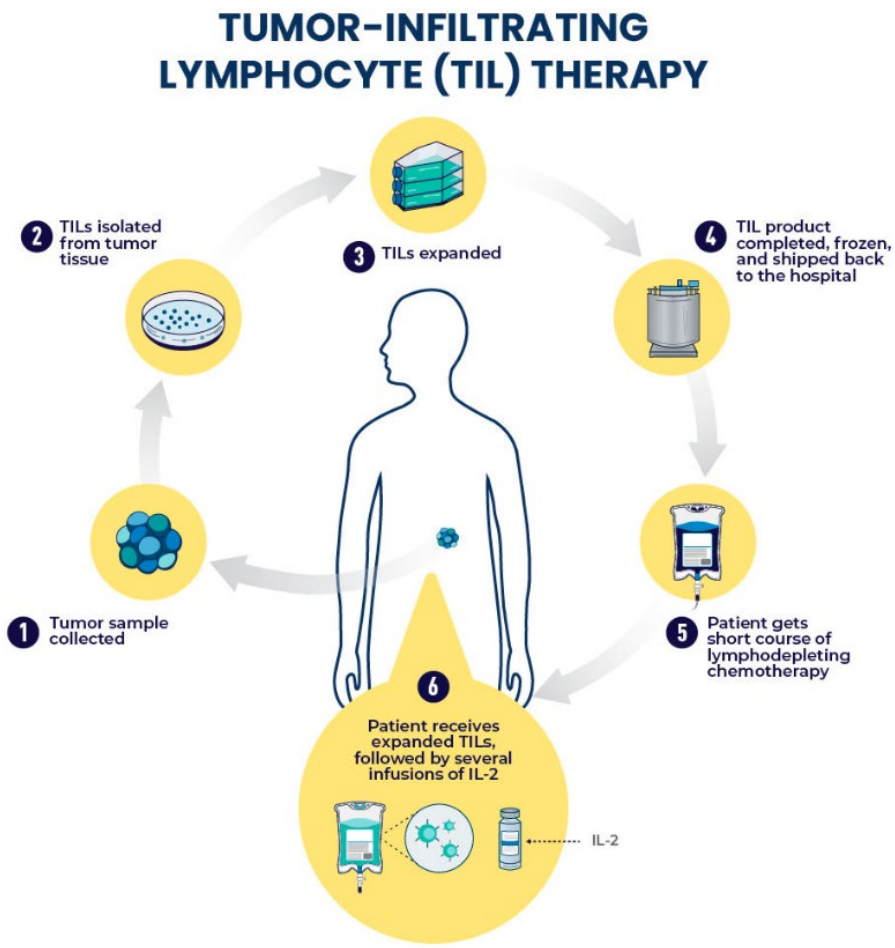
Lifileucel is a patient-specific treatment
Lifileucel is a treatment which is manufactured for every patient individually. The steps of the process with lifileucel treatment is summarised in Figure 1.

The process begins with the extraction of tumour-infiltrating lymphocytes (TILs), a type of cancer-fighting immune cell, from the patient's tumour. TILs are then sent to a specialised laboratory for expansion, where they are combined with interleukin-2 (IL-2), which promotes development of the immune system. Over several weeks, the TILs multiply into billions, creating a robust population capable of targeting and destroying cancer cells.[41] Before infusion back into the

patient, a lymphodepleting chemotherapy regimen is administered to prepare the body to receive the TIL and eliminate any suppressive cells. This crucial step optimises the environment for the infused TILs to thrive, ensuring they can function effectively against the cancer. Following treatment with lymphodepleting regimen, the expanded TIL in lifileucel are infused back into the patient, followed by a short course of high-dose IL-2 to enhance the TIL survival in the body.

Once reintroduced, the TILs target cancer by recognising specific markers, called neoantigens, on tumour cells. Once a TIL binds to these neoantigens, toxins are released to destroy the cancer cells. This individualised approach harnesses the patient's own immune system, offering a one time treatment to effectively combat cancer.

Figure 1: Process of TIL therapy production



IL-2; interleukin-2; TIL – tumour-infiltrating lymphocytes

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.
No. Lifileucel is not intended to be used in combination with any other medicines However, lifileucel is given as part of a cell therapy regimen consisting of three steps: lymphodepleting chemotherapy, lifileucel infusion, and ending with a short course of IL-2. Please see section 3c for further details.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
Lifileucel will be administered in a specialised treatment centre under the supervision of a specialist physician experience in the use of anticancer agents. An intensive care facility and specialists skilled in cardiopulmonary or intensive care medicine must be available during the administration of lifileucel.[1] Given the requirement for a specialist centre provision, patients may have to travel to receive this one-time treatment. Lifileucel is manufactured from tumour tissues that has been surgically removed from one or more tumour lesions. Therefore, patients may be required to stay at the hospital for 1 to 2 days for the tumour extraction surgery. Immune cells derived from a patient's tumour(s) are expanded in cell culture, washed, formulated as a cell dispersion, and cryopreserved (frozen at extremely low temperatures). Once manufacturing is complete, the product must pass a sterility test before release for shipping as a frozen dispersion) back to the authorised treatment centre. The product is thawed prior to administration back into the same patient. The median time from tumour tissue surgery to the end of the manufacturing process is ~23 days and to infusion is ~34 days.[1] Lifileucel is administered in a 3-step procedure with approximately an 11-day duration as shown in Figure 1[1]: 1. Lymphodepletion – Prior to getting lifileucel patients receive a type of chemotherapy known as lymphodepleting chemotherapy. This treatment helps remove suppressive cells that could interfere with the actual lifileucel treatment and prepare the body for new immune cells. Lymphodepleting chemotherapy consists of two different drugs and is given over 7 days. 2. Lifileucel infusion - Lifileucel has to be infused 24-96 hours following lymphodepletion therapy. 3. IL-2 - Within 24 hours after lifileucel infusion, IL-2 is administered every 8-12 hours for up to a maximum of 6 doses to support lifileucel T cell activity within the body. IL-2 requires a period of monitoring in a hospital setting for patients . Lifileucel is administered as a single dose of 7.5 x 10^9 to 72 x 10^9 viable cells dispersed 1 to 4 bags for IV infusion. Compared to other treatments for advanced melanoma, such as chemotherapy and ipilimumab, which require multiple doses of infusion over time, lifileucel is a one-time treatment. Patients may need to stay in the hospital for tumour extraction surgery. Then, to receive lifileucel and IL-2 and for post-treatment monitoring, patients need to remain in the hospital, however this one-time,

single-treatment process offers greater convenience for both patients and their caregivers compared to chemotherapy and ipilimumab. This eliminates the need for repeated hospital visits for ongoing treatment cycles, making lifileucel a significantly more efficient and less burdensome option. The absence of the need for subsequent hospital visits has also positive societal implications by reducing loss of productivity.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The key trial that evaluated the benefits and safety of lifileucel was the C-144-01 study. This is a multi-cohort, Phase II study in adults with advanced melanoma who had previously received at least one prior therapy, including a PD-1 therapy (i.e. nivolumab or pembrolizumab) or a BRAF inhibitor with or without a MEK inhibitor (i.e. BRAF inhibitors such as dabrafenib or vemurafenib; MEK inhibitors such as trametinib or binimetinib) in case of positive BRAF-mutation.[42]

A summary of the C-144-01 trial is provided in **Table 1**. This information was taken from Clinicaltrials.gov website (www.clinical trials.gov) on 31 January 2025.[42]

Table 1: Summary of C-144-01 trial

Study name	**C-144-01; NCT02360579**
Trial design	Global, Phase II, open-label, multicohort, multicentre, single-arm trial
Location	France, Germany, Hungary, Italy, Spain, Switzerland, the USA, and the UK
Population	Adult patients with unresectable or metastatic (advanced) melanoma treated with ≥1 systemic prior therapy including a PD-1 blocking antibody; and if BRAF V600 mutation-positive, a BRAF inhibitor or BRAF inhibitor in combination MEK inhibitor
Patient group size	Actual enrolment: 178
Key inclusion criteria	• Had diagnosis of unresectable or metastatic melanoma (Stage IIIc or Stage IV) • Progressed following ≥ 1 prior 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 • At least 1 measurable target lesion • At least 1 resectable lesion of a minimum 1.5 cm in diameter post-resection to generate TIL • Were ≥ 18 years of age at the time of consent. Enrollment of patients > 70 years of age may have been allowed after consultation with the Medical Monitor • Had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (i.e. patients who have no symptoms or are symptomatic but able to walk/not confined to bedrest) and an estimated life expectancy of≥ 3 months
Key exclusion criteria	• Were BRAF mutation positive (V600), but had not received prior systemic therapy with a BRAF inhibitor alone or a BRAF inhibitor in combination with a MEK inhibitor • Had received an organ allograft or prior cell transfer therapy • Had melanoma of uveal/ocular origin

	• Had a history of hypersensitivity to any component or excipient of lifileucel or other study drugs • Had symptomatic and/or untreated brain metastases • Were on chronic systemic steroid therapy for any reason
Expected completion date	Completed of last database lock on 24 October 2024; the trial is still ongoing.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MEK, Mitogen-activated extracellular signal-regulated kinase; PD-1, Programmed cell death protein-1.

Further information/ publications for C-144-01:
Clinicaltrials.gov (NCT02360579)[42] - https://www.clinicaltrials.gov/study/NCT02360579
Publication (Chesney et al. 2022)[41] –https://jitc.bmj.com/content/10/12/e005755

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

C-144-01 is a prospective, multicentre Phase II study in a population of patients with metastatic (advanced) melanoma after they have already received immune checkpoint inhibitors and targeted therapy.[42] Within the trial, there were four cohorts of patients (Cohort 1 to 4). Cohort 1 included patients with non-cryopreserved lifileucel which is no longer in clinical use, and Cohort 3 included retreated patients which is not included in the current license; as such, the relevant population in taken from Cohorts 2 and 4 (N=153). The discussion of how well lifileucel works in treating advanced melanoma (efficacy) will focus on the results from Cohort 4 only (N=73).

Primary endpoint: Objective response rate (ORR)
The primary endpoint of the trial was ORR, i.e. the percentage of patients who experience a significant reduction or disappearance of their tumours after treatment. In Cohort 4 of this trial, 31.5% of patients treated with lifileucel achieved this.[1]

Secondary endpoint: Duration of response (DOR)
The DOR refers to how long patients who responded to treatment continued to have this response (i.e., their tumours did not grow in size), either shrinking or disappearance of the tumour. Among the third of patients who responded to lifileucel treatment, over 50% were still responding and did not have their cancer grow in size after 1.5 years (18 months).[1] Approximately a fifth of patients (20.8%) maintained a DOR for at least 4 years.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

As presented above, the efficacy data within the lifileucel trial highlights the potential for this treatment to provide enhanced and durable responses within this patient population. Importantly, lifileucel also has the potential for a statistical cure in patients with advanced melanoma. Such meaningful responses and the hope of survival will likely result in an improved quality of life for both patients and their caregivers. Furthermore, due to lifileucel being given as a single infusion, rather than a prolonged course of therapy as with other treatments, it is expected that this will also improve patient and caregiver quality of life.

Notably, lifileucel has also demonstrated a tolerable safety profile, with most adverse events seen within the first two weeks. Again, the impact of a safe and effective treatment should not be underestimated.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Lifileucel has shown to have manageable safety profile with most adverse events occurring within the first two weeks of treatment.[40,41] The reported frequency of adverse reactions associated with lifileucel treatment were consistent with the known safety profiles of lymphodepletion chemotherapy and IL-2. The frequency of new on-set adverse events was reduced after the first two weeks following lifileucel infusion.

According to the US Prescribing Information for lifileucel, the most common adverse reactions (any-grade) with incidence of 20% or more include chills, pyrexia (fever), fatigue, tachycardia (increased heart rate), diarrhoea, febrile neutropenia (fever or infection with an abnormally low number of neutrophils in the blood), oedema (swelling), rash, hypotension, alopecia, infection, hypoxia (low oxygen levels) and dyspnea (shortness of breath).[1]

Serious adverse reactions included:

- Treatment-related mortality
- Prolonged severe cytopenia
- Internal organ haemorrhage
- Severe infection
- Cardiac disorder
- Respiratory failure
- Acute renal failure
- Hypersensitivity reactions

The adverse reactions listed included exposure to lifileucel within a regimen that included lymphodepletion chemotherapy and IL-2 infusion as described in **Section 3c**. Adverse events occurred from lifileucel infusion to 6 months post infusion.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Advanced (stage IIIc-IV) melanoma is known to have poor long-term outlook. Due to transformation of front-line treatment of advanced melanoma, patients often receive effective treatment options (e.g. immune-checkpoint inhibitors, targeted therapies) as first line treatment of advanced melanoma. Given patients cannot be re-treated in the UK, there are currently limited and mostly ineffective treatment options at the second line or beyond treatment of advanced melanoma. Chemotherapy and best supportive care are mainly used for managing symptoms and do not have curative effect or lead to sustained long-term survival. Despite advances in first-line treatment of advanced melanoma, most patients do not achieve long-term benefit, and current survival estimates are poor, ranging from 4.0 to 12.3 months.[15,16]

The results of the C-144-01 trial highlight the potential of lifileucel to delay disease progression over an extended period while keeping patients who respond to treatment in response for distinctively long-times and reduce symptoms. Given the demonstrated results, lifileucel has the potential to provide a statistical cure to these patients; UK clinical experts also agree with this statement.[43] .[43]

Another major clinical advantage of lifileucel is its ability to target multiple neoantigens on tumour cells, which is a distinguishing feature from other therapies that focus on targeting a single neoantigen allowing lifileucel to target the tumour even if it mutates. By using the patient's own TIL, lifileucel also minimises the risk of adverse immune reactions, such as graft-versus-host disease, commonly associated with other cell-based therapies and occurs when infused cells (the graft) see the healthy tissues in the patient's body (the host) as foreign and attacks them.

Moreover, the one-time administration of lifileucel offers substantial logistical benefits. It reduces the treatment burden for patients compared to traditional treatments that require ongoing, frequent administration with intravenous infusion. It also minimises the risk of cumulative side effects often associated with prolonged treatment regimen, which in turn can further improve patients' QoL.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Patients undergoing lifileucel therapy may experience adverse events from the pre-lifileucel regimen (lymphodepleting regimen) and post-lifileucel regimen (IL-2). However, lifileucel has shown a safety profile that is consistent with what is expected with lymphodepleting chemotherapy and IL-2 treatment (**Section 3g**).

Lifileucel treatment must be given at a specialist centre. Therefore, patients may need to travel farther than they would for conventional treatments, as the specialist centre may not be local; however this extended travel is only a single time necessity due to one-off administration of lifileucel.

As lifileucel is a newer treatment option compared to currently available regimens, there is less publicly available information and data around the benefits and side effects of treatment. As such, patients may have some discomfort around using such a new treatment.

Finally, the interval from the tissue collection until lifileucel administration (30 days or more) may result in adverse health outcomes and can induce anxiety for patients, affecting their emotional and physical wellbeing compared to conventional treatments which can be initiated quicker.

No other key disadvantages of using lifileucel were identified for patients, caregivers, or their communities when compared to the current treatments for patients with previously advanced melanoma.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

The manufacturer developed a health economic model with data from the C-144-01 study along with published literature.[44,45] The model compares survival, QoL and costs for patients who would be suitable for treatment with lifileucel compared with established treatments in the UK clinical practice i.e., ipilimumab, chemotherapy and best supportive care.

The model consists of three health states to reflect the typical disease progression of patients with advanced melanoma:

- Progression-free
- Progressed disease
- Death

All patients enter the model in the 'progression-free' health state, indicating that they have no disease progression at the start of treatment. Over time, the disease may progress and when this occurs, the patient transitions out of the 'progression-free' health state and enters the

'progressed disease' health state in the model. If a patient dies, they transition to the 'death' health state.

Each health state is linked with a QoL score (referred to as 'utility'), survival and healthcare resource use and costs. Transitions in the model from one health state to the next health state are irreversible. This means that once a patient progresses to 'progressed disease', they cannot go back to 'progression-free' health state. This is a reasonable medical assumption because tumour will not shrink on its own without treatment. And if treatment is given, the patient moves to the next stage of care, which is different from the current 'progression-free' state.

Modelling how much a treatment extends life

As detailed in **Section 3e**, lifileucel is expected to delay disease progression over an extended period of time with a potential of a curative outcome. Survival data for lifileucel in the model is based on the overall survival (the length of time a patient lives after starting treatment) and progression-free survival (the length of time a patient lives without the disease getting worse after starting treatment) data observed in the C-114-01 trial, with a median follow-up of 48.1 months.[40] Survival data for the comparators (ipilimumab, chemotherapy and best supportive care) are based on published literature.[44,45] As detailed in **Section 3e**, lifileucel is expected to delay disease progression over an extended period of time with a potential of a curative outcome.

The economic model simulates the trajectory of the disease from the second line treatment of melanoma until patients' death. This time horizon is longer than the length of the follow-up in C-144-01 trial. Additionally, the model estimates that a proportion of patients receiving lifileucel is expected to be long-term survivors, with survival rate similar to the general population.

The effectiveness of ipilimumab versus lifileucel was assessed using an indirect treatment comparison, which adjusted for key factors that could influence outcomes between the two groups. Additionally, a simple (naïve) comparison of lifileucel with chemotherapy and best supportive care was conducted to help interpret the efficacy results. Compared to current therapies; ipilimumab, chemotherapies and best supportive care, the model shows that patients treated with lifileucel would have up to 4 additional years of life..

Modelling how much a treatment improves QoL

While the QoL data from the trial does not provide direct comparative insights into QoL (described in Section B.3.4 of Document B), it suggests that patients treated with lifileucel may experience an improved QoL due to high response rates, curative potential, and a longer duration of response. These allow patients to remain progression-free for an extended period compared to other treatments (ipilimumab, chemotherapy or best supportive care). Additionally, the one-time lifileucel treatment reduces the need for frequent hospital and clinic visits, further enhancing patient's overall well-being. Although the QoL data were not obtained from the trial to be utilised in the economic model, the average utility scores estimated for each health state was comparable to the average pre-progression and post-progression utility scores reported in other trials within the same setting.

Each health state has an associated QoL. This means that how well a patient feels depends on what stage of the disease they are in. The QoL is influenced by how long the patient live without the disease getting worse, known as progression-free survival and how long they survive, known as overall survival.

A fraction of patients is expected to be long-term survivors with minimal risk of disease-related death and no progression throughout their lifetime, which, in turn enhances their QoL. Since the

model does not incorporate response rates or duration of response (DoR) data, it primarily focuses on disease progression rather than a patient's response to lifileucel. As a result, long-term benefits from a sustained response, such as improved QoL and potential delays in symptom worsening are not fully captured in the QoL assessments within the model. This means that patients who experience prolonged responses to lifileucel may benefit more than what is reflected in the model's projections.

Modelling how the costs of treatment differ with the new treatment
For lifileucel and each comparator, the model accounts for comprehensive range of costs due to drug acquisition, drug administration, adverse events, healthcare resource use , and end-of-life care. Drug acquisition and administration costs for lifileucel include the one-off treatment cost, as well as pre-treatment (i.e. lymphodepleting chemotherapy) and post-treatment (IL-2) costs. No drug acquisition or administration cost were associated with best supportive care as it involves only disease and symptom management. For further details, please refer to the company submission, Section 3.4.

Uncertainty
There is a lack of randomised studies comparing lifileucel with the comparators, which creates some uncertainties in the clinical data used for the economic model. To estimate how these treatments compare in effectiveness, indirect comparisons were conducted and further explained in the company submission, section 2.9 and Section 3.3.1.

Every effort has been made to reduce the impact of uncertainties in the economic model, including discussion and validation of the methods and assumptions used with leading UK melanoma medical specialists.

Key uncertainties in the model include:

- **Long-term survival outcomes for lifileucel.** Whilst mature survival data for lifileucel are available, there is a need to estimate clinical outcomes over a lifetime horizon, utilising the 4-year follow-up of the C-144-01 trial. The four-year data while substantial, represents a small proportion of a patient's further lifetime and therefore long-term extrapolation may introduce uncertainty. This uncertainty was addressed through the validation of the extrapolation approaches, outcomes and base case survival distribution choices with UK clinical experts. Additionally, scenario analyses were performed to reflect alternative approaches and survival distributions.
- **Limited survival data are available for ipilimumab and chemotherapy.** Literature identified for both ipilimumab and chemotherapy reported relatively short duration of follow-up. These data were extrapolated over a lifetime horizon which introduced uncertainty. This uncertainty was addressed with UK clinical experts. Additionally, scenario analyses were performed to reflect alternative approaches and survival distributions.
- **No survival data for BSC were identified.** As no survival data for best supportive care were identified, UK clinical experts' opinion were sought to address this uncertainty.
- **The generalisability to the UK.** Cohorts 2 and 4 of the C-144-01 trial were pooled despite differences in patient characteristics (described further in Section B.2.2.3). Additionally, the patients in the cohorts predominantly represented those in the United States, introducing uncertainty of whether C-144-01 cohorts are reflective of UK clinical practice. The pooling of Cohorts 2 and 4 as well as the trial's reflectiveness of the UK was validated by UK clinical experts.
- **Limited HRQoL data.** There were limited HRQoL data collected from the C-144-01 trial. Therefore, values used to measure the QoL were derived from published literature.

Cost-effectiveness results
The cost-effectiveness results for lifileucel compared with ipilimumab, chemotherapy and best supportive care are presented in section 3.9 of the company submission using a measure called the incremental cost-effectiveness ratio (ICER). The ICER calculates how much it costs to gain an extra year of good health known as Quality Adjusted Life Years (QALYs) with lifileucel versus the comparators (ipilimumab, chemotherapy or best supportive care).

Overall, the analysis shows that lifileucel helps patients to live longer by prolonging survival, improves their quality of life, resulting in greater QALYs more than the current treatments (ipilumumab, chemotherapy or best supportive care). Treatment with lifileucel is also associated with additional costs as it is a new and innovative medicine compared with current treatments.

Additional factors
Previously, a decision modifier called the "end-of-life" criteria was used by NICE to assess the value of treatments for diseases with poor life expectancy. If the "end-of-life" criteria were met, where patients with disease were expected to live less than 24 months and the treatment was likely to extend their life beyond 3 months, the NHS would consider treatments with higher costs. In this case, treatments costing up to £50,000 for each additional year of healthy life gained (QALY) would be regarded as cost-effective.[46]
Lifileucel meets the previous "end-of-life" criteria:

- **Lifileucel is for patients with short life expectancy of less the 24 months**: Advanced melanoma has a poor outlook where patient's life expectancy will likely be less than one year after disease progression. Studies show that the median survival is about 9 months for ipilimumab, 6 months with chemotherapy and likely even shorter with best supportive care.
- **Lifileucel extends life by over 3 months compared with current standard of care:** There is sufficient evidence to indicate that lifileucel offers an extension of life, normally of at least an additional 3 months compared to current NHS treatment. The median survival of lifileucel from the C-144-01 trial has shown that lifileucel offers an extension of life more than 3 months compared with the comparators.

However, the "end-of-life" criteria was replaced with the severity modifier as part of its Methods and Process update in 2022.[47] The severity modifier reflects how much society values the most serious and life-limiting diseases by comparing how many years of healthy life (QALYs) people with these conditions have left, based on current treatment, to the average person of the same age and sex in the UK.

There are two severity modifiers: the 1.2x modifier and the 1.7x modifier. The 1.7x modifier indicates a more serious condition than the 1.2x modifier. Using either modifier means the extra benefit in QALYs from a treatment like lifileucel is multiplied by 1.2 or 1.7, depending on the modifier. While the severity modifier is technically a way to adjust QALYs, it can also be thought of as raising the amount the NHS is willing to pay for treatments. For example, the 1.2x modifier increases the NHS's threshold from £30,000 per QALY to £36,000 per QALY, and the 1.7x modifier raises it to £51,000 per QALY, similar to the previous threshold for "end-of-life" treatments.

As described in detail in Section 3.6 of the company submission, lifileucel is likely qualify for the 1.7x severity modifier when compared to chemotherapy and best supportive care, and 1.2 modifier when compared to ipilimumab, based on the QALY calculations. However, when considering current UK treatment practices and the market share of each treatment group, lifileucel may also meet the criteria for a 1.7 severity modified compared to ipilimumab.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations. If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)
There are currently no licensed TIL cell therapy treatments for patients with advanced melanoma. Lifileucel is therefore highly innovative, representing a "step-change" for patients and their families. It is the first and only treatment of its kind, offering a one-off, individualised therapy developed from patient's own immune cells. Caregivers of patients with advanced melanoma are also indirectly burdened by the disease (**Section 2d**). Whilst this is not captured in the economic model as it measures the economic value of lifileucel from a payer's perspective, rather than a societal perspective, lifileucel treatment is expected to improve the QoL of caregivers by reducing patients' demands from the caregivers due to improvements in their own QoL. Additionally, lifileucel offers economic benefits to society, both directly and indirectly, by enabling patients to return to the work force, supporting normal daily living and reducing healthcare burdens. With the possibility of statistical cure, patients responding to treatment may adapt a healthier lifestyle which could further improve their survival.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
The company is not aware of any equality issues at this time for lifileucel in this indication. Lifileucel should be made available to all eligible patients in the UK.

<u>**SECTION 4:** Further information, glossary and references</u>

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
• What is melanoma skin cancer? Available here: https://www.cancerresearchuk.org/about-cancer/melanoma • Melanoma skin cancer incidence by gender and UK country. Available here:

https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/melanoma-skin-cancer/incidence#heading-Zero

- Efficacy and safety of lifileucel. Available here: https://jitc.bmj.com/content/10/12/e005755

- C-144-01 clinical trial. Available here: https://www.clinicaltrials.gov/study/NCT02360579

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

Patient groups and charities:

- Melanoma focus: https://melanomafocus.org/
- Melanoma UK: https://www.melanomauk.org.uk/
- Melanoma fund: https://melanoma-fund.co.uk/

4b) Glossary of terms

- **EQ-5D:** EuroQol-5 Dimensions is a tool to measure the quality of life of a person, based on their responses to questions covering mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. EQ-5D is NICE's preferred QoL measure and is scored from a scale of 0–1, with 0 denoting death and 1 denoting perfect health.
- **EORTC QLQ-C30:** EORTC QLQ-C30 is a widely used instrument to measure of quality of life in cancer patients. It includes 30 questions assessing physical, emotional, and social well-being, as well as symptoms like pain and fatigue. Scores range from 0 to 100, with higher scores for functioning scales indicating better health and higher scores for symptom scales indicating worse symptoms.
- **ICER:** The incremental cost-effectiveness ratio is calculated by dividing the difference in total expected costs by the difference in expected health outcomes for an intervention (e.g.lifileucel) versus a comparator (e.g. best supportive care). It provides a value of the resources per unit of the health effect.
- **Metastatic**: Spread of cancer from the primary site to other parts of the body.

- **Overall response rate (ORR):** ORR is the percentage of patients whose cancer responds to treatment in one of two ways; either a partial response, where the tumour shrinks by at least 30%, or complete response, where the tumour completely disappears with no signs of cancer after treatment.
- **Overall survival (OS**): OS is the length of time that patients diagnosed with a disease remain alive from the date of diagnosis, the start of treatment or from the time of randomization in clinical trial settings.
- **Prognosis**: A probable course or outcome of a disease.
- **Progression-free survival (PFS**): PFS is measured as the length of time from the date of diagnosis, the start of treatment or from the time of randomization in clinical trial settings until disease progression (i.e. tumour growth) or death, whichever occurs sooner.
- **Quality-adjusted life year (QALY):** The QALY is a standardised unit of measure of the state of health of a person or group in which remaining years of life are adjusted to reflect the QoL. One QALY is equal to 1 year of life in perfect health.
- **Quality of life (QoL):** The QoL refers to how well a person feels and functions in daily life.
- **Utility:** The measure of the preference or value that an individual or society associates by living in a health state. Utility is usually scored from 0–1, with 0 indicating death or worst possible health state and 1 reflecting perfect health.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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47. National Institute for Health and Care Excellence (NICE). PMG36: NICE health technology evaluations: the manual [Internet]. 2023 [cited 2024 Jul 9]. Available from: https://www.nice.org.uk/process/pmg36/chapter/economic-evaluation

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Lifileucel for previously treated unresectable or metastatic melanoma [ID3863]

Clarification questions

March 2025

File name	Version	Contains confidential information	Date
ID3863 Lifileucel for melanoma – EAG clarification letter_29Apr25	1.0	Yes/no	29 April 2025

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

Intervention and comparators

A1. Company's submission (CS), Section 1.2, Table 2, page 11. The US Food and Drug Administration (FDA) clinical review (https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/amtagvi) highlights some challenges in manufacturing lifileucel in the C-144-01 study (including product quality concerns), and the substantial time between initial tissue collection and final treatment, which may impact patient eligibility. Given these issues, please clarify how these challenges can be effectively managed within the NHS framework within England & Wales.

Response: Manufacturing of lifileucel currently takes 22 days, with up to 14 days before product receipt at an authorized treatment centre. Due to these timelines for manufacturing and product availability, we recommend that physicians consider the following criteria for patient eligibility: ECOG status at 0 or 1, and life expectancy ≥ 3 months.

Lifileucel commercial product in the United States that is manufactured outside of the commercial dose range (as specified by the FDA) is currently offered at no charge under the expanded access protocol IOV-EAP 402, if the Company believes the

product is still safe and if desired by the treating physician. The Company expects to offer this same expanded access protocol or similar to England and Wales if the NHS agrees that this is beneficial for patients.

A2. CS, Section 1.1, Table 1, page 9. The CS includes three comparators: ipilimumab monotherapy, chemotherapy and BSC. The CS explains that clinical guidelines published by the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) recommend the use of nivolumab plus ipilimumab combination therapy as first-line treatment, and that ipilimumab would not be used again at a subsequent line of therapy. Given these two factors, please comment on the relevance of ipilimumab monotherapy as a comparator for lifileucel.

Response: Patients who are treated with ipilimumab and nivolumab as first-line treatment (and after treatment with BRAF/MEK inhibitor if BRAF-mutated) do not have the option of ipilimumab monotherapy as a subsequent treatment in the UK. These patients, typically have the option of best supportive care, clinical trials, or chemotherapy. As the manufacturer understands, best supportive care and chemotherapy are not typically acceptable as a primary comparator for NICE evaluations, and enrolment in clinical trials is not considered a comparator for the purposes of the evaluation. Use of chemotherapy as a primary comparator is also problematic as usage is currently very low. In the TA950 committee discussion focused on 2L treatment for metastatic melanoma, chemotherapy was not even mentioned as a possible option (section 3.11). The perception that chemotherapy is an inappropriate comparator was expressed by key opinion leaders talked to by the manufacturer due to low usage and perceptions of low effectiveness. Furthermore, based on the advisory board conducted by the Company, the same key opinion leaders also indicate that not all patients receive nivolumab plus ipilimumab as a first line treatment, which leaves ipilimumab as a potential second line treatments, especially for patients who are treated anti-PD1 monotherapies (e.g. pembrolizumab, nivolumab) in 1L. With these considerations, the Company continues to believe that ipilimumab remains the best

comparator for this evaluation. The lack of appropriate treatment options reflects the high unmet need for this patient population in the UK.

A3. CS, Section 1.1, Table 1, page 9. In the company's opinion, what is the main comparator for lifileucel - ipilimumab monotherapy, chemotherapy or best supportive care (BSC)?

Response: Ipilimumab monotherapy is the main comparator for lifileucel.

Evidence searches for clinical and economic systematic literature reviews (SLRs)

A4. CS, Appendix B.3, page 28, Appendix E2.1, page 106, Appendix F2.2., page 130, and Appendix G2.1, page 155. The CS appendices state that one of the databases searched was "PubMED-not-MEDLINE." Please clarify exactly what source this refers to, and provide details of the searches performed on this database, including the platform used to access it and the search terms used.

Response: The Company apologises for the unclear reporting and wishes to clarify that PubMED-not-MEDLINE was not part of this SLR. The search was undertaken using http://embase.com advanced search. Embase (Excerpta Medica Database) is the core database of Embase, and it also includes a MEDLINE supplement, covering all MEDLINE records which are the core of PubMed. It should be noted that a limited set of publications from PubMed may not be included in Embase (e.g., "MEDLINE in-process" or "ahead-of-print" citations), however, this was deemed to have a limited impact on the searches. The clinical review question also included Cochrane CENTRAL, Cochrane Clinical Answers and Cochrane Database of Systematic Reviews (CDSR) searches, using https://www.cochranelibrary.com/advanced-search. The search terms used were reported in Appendix B (Table 2 [Embase] and Table 3 [Cochrane]), Appendix E (Table 17), Appendix F (Table 25) and Appendix G (Table 32).

A5. CS, Appendix B.3, page 28 and Appendix B.3.2, Table 3, pages 33-35. The text on page 28 states that searches were conducted in Cochrane Database of Systematic Reviews (CDSR); however, Table 3 presents a search strategy only for CENTRAL and

Cochrane Clinical Answers. Please explain the discrepancy in the reporting and clarify whether the CDSR was searched.

Response: The Company acknowledges that the heading of Table 3 is incorrect, the search did cover CDSR as well as CENTRAL and Clinical Answers and Table 3 presents the search strategy for all. Three reviews were identified from CDSR, all of which were excluded at first pass (Zhu *et al.* 2021 – DOI: 10.1002/14651858.CD011300.pub3, Dinnes *et al.* 2019 – DOI: 10.1002/14651858.CD012806.pub2, Pasquali *et al.* 2018 – DOI: 10.1002/14651858.CD011123.pub2).

A6. CS, Appendix B.3.2, Table 2, pages 31-33. The searches of MEDLINE and Embase appear to have been conducted simultaneously but without changing the subject headings (MeSH or Emtree) as appropriate to suit each database. Please clarify how the searches were conducted in these databases and comment on the possible implications for retrieval.

Response: As stated in A4, the search was undertaken using http://embase.com. Embase includes a MEDLINE supplement, covering all MEDLINE records.

A7. CS, Appendix E.2.1, page 106, Appendix F.2.2, page 130, and Appendix G.2.1, page 155. Please clarify whether any relevant economics-focused databases, such as the NHS Economic Evaluation Database (NHS EED), the international Health Technology Assessment (HTA) Database from the International Network of Agencies for Health Technology Assessment (INAHTA) or EconLit, were searched for the SLRs covering studies of cost-effectiveness, health-related quality of life (HRQoL), or cost and health care resource use.

Response: The Company adopted a comprehensive approach that aligned with the University of York Centre for Reviews and Dissemination (CRD) guidelines (https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf). The searches for the submission included the CRD database, which contains NHS EED, HTA and the Database of Abstracts of Reviews of Effects (DARE). CRD searches were undertaken from 2014 onwards. A total of 14 records were identified, however none were deemed relevant for inclusion in the SLR as they were all either covering incorrect populations (n=7), intervention/comparators (n=5) or outcomes (n=2).

A8. CS, Appendix E.2.1, pages 106-107, Appendix F.2.2, pages 130-131, and Appendix G.2.1, page 156. Regarding the supplementary sources that were searched for the economic (cost-effectiveness, HRQoL, and cost and health care resource use) SLRs:

- Please explain the discrepancy between the congresses listed for searches for HRQoL studies in Appendix F.2.2 compared to searches for cost-effectiveness and cost and health care resource use studies (Appendices E.2.1 and G.2.1, respectively).
- Please explain the rationale behind the choice of sources listed, in particular congresses related to haematology medical societies and associations (Appendices E.2.2 and G.2.1) and the World Health Organisation International Clinical Trials Registry Platform (Appendices F.2.2 and G.2.1).
- Please also comment on the omission of Health Technology Assessment International (HTAi) as a supplementary source for conference abstracts, especially given that ISPOR has been included.

Response: On the discrepancy between listed congresses, the Company apologises for the error – the correct list of congresses reviewed for each of the review questions are:

- The Professional Society for Health Economics and Outcomes Research (ISPOR)
- European Society for Medical Oncology (ESMO)
- The Society for Melanoma Research (SMR)
- American Society of Clinical Oncology (ASCO)
- The Society for Immunotherapy of Cancer (SITC)

The World Health Organisation International Clinical Trials Registry Platform in the searches was included solely for completeness. Regarding HTAi, the expectation was that ISPOR would cover relevant abstracts and that an HTAi search would render, if anything, only abstracts similar to the ISPOR ones, e.g., reporting from the same studies as the abstracts identified from ISPOR. However, to ensure completeness, an add-on search was conducted as part of this response, whereby HTAi abstracts from the past three years (2022-2025) were reviewed. No relevant abstracts were identified.

A9. CS, Appendix B.3.2, Tables 2 (page 32) and Table 3 (page 34), Appendix E.2.1, Table 16 (page 107) and Table 17 (page 109), Appendix F.2.2, Table 24 (page 131) and Table 25 (page 133), and Appendix G.2.1, Table 31 (page 157) and Table 31 (pages 158-159). Regarding search terms included in the searches for all SLRs (clinical and economic-related):

- Please comment on the rationale for including outcome search terms in the search strategies, and the implications for retrieval, given recommendations from SuReInfo (Arber *et al.* 2024 - https://sites.google.com/york.ac.uk/sureinfo/home/search-strategy-development) to not include the Outcome element of a PICO-style question framing.
- Search terms have been used to identify studies of the types eligible for inclusion in the SLRs (clinical trials and observational studies for the clinical effectiveness SLR; cost-effectiveness, HRQoL and health care resource use (HCRU) for the economic SLRs). However, there is no indication in the reporting that these are based on published filters which have been validated for sensitivity/precision in identifying eligible studies. Please indicate whether this was the case (providing a supporting citation to relevant validation studies).

Response:

a) The searches were developed iteratively, whereby different scenarios were tested, including without outcomes search terms. A sample of hits identified with the searches without the outcomes filters was screened. It was found that omitting the outcomes filters led to the inclusion of an excessive number of irrelevant publications. To limit the number of irrelevant hits and to focus on the most applicable papers, the company decided to include outcomes filters in the searches. Furthermore, considering the breadth of the outcome filters (over 3 million hits for the clinical outcomes filter, 1.2 million hits for the economic filter, 1.3 million hits for the quality of life/utility filter, and almost 11 million hits for the resource use filter), it is highly unlikely that any key publications were overlooked as a consequence of these filters.

b) The Company wishes to clarify that the filters are based on the following published filters:

a. RCT filter, observational study filter, economic filter: Scottish Intercollegiate Guidelines Network (SIGN)
b. Quality of life filter (Arber *et al.* 2015 – https://abstracts.cochrane.org/2015-vienna/sensitivity-search-filter-designed-identify-studies-reporting-health-state-utility)

A10. CS, Appendix B.3, page 28 and Table 1 (page 30), Appendix E.2.1, page 106, Table 16 (page 108) and Table 17 (page 109), Appendix F.2.2, page 130, Table 24 (page 132) and Table 25 (page 134), and Appendix G.2.1, page 155-156, Table 31 (page 157) and Table 32 (page 159). Please clarify the rationale behind limiting the electronic database searches to 2014 and later given that there is potentially relevant evidence dating from before 2014 relating to treatments that are being considered as comparators in this submission (e.g., the Hodi *et al.* 2010 study of ipilimumab - doi:10.1056/NEJMoa1003466).

Response: Search criteria were restricted to publications from 2014 onwards, which coincides with the introduction of programmed death-1 (PD-1) inhibitors in melanoma. This ensured that the review only captured publications concerning the relevant, current treatment landscape.

A11. CS, Appendix B.4.1, Figure 1 (page 37), Appendix E.4.1, Figure 8 (page 112), Appendix F.3.1, Figure 9 (page 136), and Appendix G.4, Figure 10 (page 161). The PRISMA diagrams presented in Figures 1 and 8-10 do not indicate clearly how many results came from each individual database searched, and for Figures 1, 9 and 10, the results from the trial register searches have been omitted or are not clearly reported. Please provide updated PRISMA diagrams with the missing or unclear information, including the final total number of included studies.

Response: The following databases were searched:

- **Clinical review question:** Embase (inclusive of MEDLINE) and Cochrane (CENTRAL, Clinical Answers and CDSR).
- **Cost-effectiveness, health-related quality of life (HRQoL), cost and healthcare resource use (HCRU) review questions:** Embase (inclusive of MEDLINE), therefore the PRISMA diagrams only include results from this database.

The clinical trial databases were reviewed as part of the grey searches for all review questions. This is all reflected in the PRISMA diagrams in the CS Appendices.

To note, if any records relevant to the cost-effectiveness, HRQoL, or HCRU review questions would have been identified during screening of the Cochrane searches for the clinical review question, they would have been included in the review question of relevance. This was not the case, as confirmed by double checking the papers excluded based on outcomes as part of this response.

SLR for clinical evidence

A12. CS, Section 2.1 pages 28-29, and CS Appendices B.3.3 and B.3.4, page 35. Please confirm if study selection, data extraction and quality assessment was undertaken independently by a minimum of two reviewers for each systematic review in the clinical and economic sections. If not, please describe and justify the approach undertaken.

Response: The Company confirms that two independent reviewers undertook the screening and study selection, with arbitration undertaken by a third reviewer. Extraction and quality assessment was performed by one reviewer, and quality controlled by a second.

A13. CS, Appendix B.3.1, Tables 1 and 2, pages 30 and 33. For completeness, please comment on the limitations and generalisability of restricting the SLR (including the indirect treatment comparison [ITC]) to English-language publications.

Response: Re-running the searches omitting the English-language filter rendered 12 additional hits, three of which were duplicates. Reviewing these hits confirmed that no relevant studies were excluded based on the language restriction, including for the ITC. The studies concerned were either the wrong study type (n=9, including the duplicates), covered an irrelevant population (n=1), comparator (n=1) or outcomes (n=1).

A14. CS, Section 2.1, Figure 4 (page 30), Section 2.2, Table 5 (pages 31-32), Section 2.10.1, Table 21 (pages 63-64), Appendix B.3.1, pages 29-30, Appendix B.4.1, pages 35-71, and Appendix B.4.5, Table 8 (pages 80-82). The text in Appendix B.3.1 appears to provide inclusion criteria for a broader systematic review which identified 48 unique

citations across 26 different studies (results reported in Appendix B.4.1). However, the text in Tables 5 and 21 (main CS) and Table 8 (Appendix B.4.5) then suggest 21 references associated with eight unique studies (one on lifileucel [14 citations], five on ipilimumab [five unique citations], and two on chemotherapy [two unique citations]). Regarding these differences:

a) Please explain the inconsistency (including reference sources) between the 'included' studies listed in Sections 2.2 and 2.10 and the 'included' studies listed in Appendix B.4. In addition, in Figure 4 the second lowest box on the left-hand side of the figure suggests that 49 (40+9) new reports were included in the review, but the box below this indicates that 48 (40+8) new reports were included. Please clarify why these numbers are different.
b) Please provide the narrower inclusion/exclusion criteria relevant to this appraisal.
c) Please confirm which studies meet the inclusion criteria for this appraisal. If further studies meet the inclusion criteria for this appraisal, in addition to the studies listed in (a), please provide them.

Response:

a) CS Section 2.2 Table 5 is a summary of the C-144-01 trial. The studies listed in CS Section 2.10 (Table 21) and Appendix B.4.5 (Table 8) refer to the subset of studies from the clinical SLR which were deemed potentially relevant for use in the ITC and which were therefore included in the feasibility assessment. The SLR identified 40 records from database searches (as detailed in Appendix B.4.1, Table 4), and eight records from the grey searches (as detailed in Appendix B.4.1, Table 5). The Company notes an error in the Table 5 caption and wishes to clarify that n=8 grey records were identified, i.e., a total of 40+8 records.
b) The records identified in the SLR were assessed for inclusion in the ITC feasibility assessment based on the following criteria:
    a. **Study location:** studies conducted at sites in Europe to ensure the analysis was conducted in a population that is representative of patients with unresectable or metastatic melanoma in the UK. Therefore, studies which were not conducted at European sites (e.g.,

US centres only) were excluded, as they may not align with UK clinical practice.

b. **Prior lines of therapy** - the patients were eligible for inclusion in the key lifileucel trial (C-144-01) if they had progressed on or after ≥1 prior systemic therapy including a PD-1 blocking antibody; and if BRAF V600 mutation-positive, have had prior therapy with a BRAF +/- MEK inhibitor (Sarnaik *et al.* 2021 – DOI: 10.1200/JCO.21.00612, Chesney *et al.* 2022 – DOI: 10.1136/jitc-2022-005755, Medina *et al.* 2023 – https://www.iovance.com/uploads/FINAL-SITC-2023_C-144-01-4-Year_Print-POS-2565-publication.pdf, C-144-01 clinical pack).

c. **Availability of PFS and OS KM plots** - PFS and OS are key efficacy outcomes of interest for the potential ITC, and KM plots are required to carry out analyses relating to PFS and OS (Jiang and Ni. 2020 – DOI: 10.1186/s12874-020-01124-6), as such, studies which did not report either a PFS or OS KM plot were excluded from the analyses.

c) A total of 48 records met the clinical SLR criteria as described in Appendix B.3.1 (Table 1). However, 21 records were included in the ITC feasibility assessment based on the criteria listed in point b), as described in Appendix B.4.5 (Table 8). No further studies to those listed in the Appendices met the SLR inclusion criteria.

A15. PRIORITY. CS, Section 2.2, page 31. The CS states that the SLR for the ITC included an eligibility criterion that studies should be *'conducted in Europe or global studies which included European sites.'*:

- Please explain the clinical relevance of this eligibility criterion and its impact (e.g., potential biases) to this systematic review;
- Given that all of Cohort 2 and approximately 70% of Cohort 4 of Study C-144-01 were from the United States of America, please clarify why this criterion was necessary (including for the ITC), and which any studies (if any) were excluded due to this criterion. Please also comment on whether these excluded studies would have been considered relevant had this criterion not been applied.

Response: This eligibility criterion was applied to ensure that the clinical evidence underpinning the ITC is relevant and generalisable to UK clinical practice. In the absence of relevant UK data, the Company considered European studies or global

studies which included European sites more relevant than ex-European sources given that the management of melanoma patients across Europe is expected to align closely with the UK setting.

The Company acknowledges that Study C-144-01 was conducted in a large number of US sites. However, applying the European-site criterion aimed to ensure comparator data incorporated into the ITC closely reflect the UK clinical practice.

Of the 40 studies that met the inclusion criteria for the SLR and were subsequently assessed for inclusion in the ITC, the majority were excluded either due to not meeting the prior line of therapy criteria (n=18) or the lack of relevant KM plots (n=14). Only two studies were excluded specifically due to not meeting the *'conducted in Europe or global studies which included European sites'* criterion: Baron *et al.* 2021 (DOI: 10.1177/1078155220924719) and Friedman *et al.* 2022 (DOI: 10.1136/jitc-2021-003853). However, these studies included only a few patients (n=22 and n=9, respectively), hence, are not considered sufficiently large to inform a robust ITC. Thus, the application of this eligibility criterion has not introduced bias affecting the robustness of the ITC results.

A16. CS, Appendix B.4.6, Table 12, pages 93-96 and Appendix K.2, Table 54, pages 208-209. Please provide further details of the Downs and Black checklist that was used to critically appraise the relevant clinical effectiveness evidence for this appraisal:

- Please clarify which version of the checklist was used;
- For each response to a signalling question, please provide supporting evidence (e.g., direct quotations from the text of the study report should be used whenever possible) and a score for the answer;
- For each study, please provide a final overall score;
- To help with the interpretation of the study's overall quality and assist in understanding the reliability of the findings, please provide an overall summary of the results.

Response: The original checklist (Downs *et al.* 1998 – DOI: 10.1136/jech.52.6.377) was used for the submission, with the common modification that the scoring of item 27 (Power) was simplified to 0 or 1, rather than the 0–5 used in the original version.

The total scores from the Downs and Black checklist for each respective clinical paper are as follows:

- Wilson *et al.* 2021 (DOI: 10.1097/CMR.0000000000000746): 16
- Mangin *et al.* 2021 (DOI: 10.1002/cam4.3760): 17
- Cybulska-Stopa *et al.* 2020 (DOI: 10.1016/j.advms.2020.05.005): 16
- Pires da Silva *et al.* 2021 (DOI: 10.1016/S1470-2045(21)00097-8): 16
- Long *et al.* 2022 (KEYNOTE-006 [DOI: 10.1016/j.annonc.2021.10.010]): 17

All five studies clearly described their objectives, outcomes, interventions, and patient characteristics, and detailed appropriate statistical methods with valid outcome measures. All studies reported variability in outcomes and all studies reported adverse events with the exception of Long *et al.* 2022 (DOI: 10.1016/j.annonc.2021.10.010), while none described the characteristics of patients lost to follow-up. Additionally, all studies reported actual probability values with the exception of Wilson *et al.* 2021 (DOI: 10.1097/CMR.0000000000000746). While participants were generally representative of their source populations, external validity was limited due to lack of reporting on treatment settings and absence of blinding. Only Long *et al.* 2022 (DOI: 10.1016/j.annonc.2021.10.010) reported randomisation of patients to intervention groups, while no studies reported on allocation concealment and adjustment for confounding. All studies reported having sufficient power to detect clinically important effects.

Clinical effectiveness evidence

A17. CS, Section 2.3.1, page 33. The CS states that *"One final efficacy data read out is expected from the trial in late-2025."* Please clarify which endpoints will be included in this final data read-out.

Response: The final efficacy data read out will report updated duration of response and overall survival, reflecting longer follow-up.

A18. CS, Section 2.3.1, Figure 5, page 32. The figure indicates that 66 patients were included in Cohort 2 and 75 patients were included in Cohort 4 (total N=141). However,

the text on page 33 indicates that 153 patients were included from Cohorts 2 and 4. Please clarify what the numbers in Figure 5 relate to.

Response: The company wish to clarify that Figure 5 shows intended enrolment, not actual enrolment. A total of 153 patients were included from Cohorts 2 and 4.

A19. CS, Section 2.3.3, page 40. The CS and the publication by Chesney *et al.* (http://dx.doi.org/10.1136/jitc-2022-005755) state that in Study C-144-01 *"...some notable differences were observed in the baseline characteristics of patients in the later-enrolled Cohort 4 compared with Cohort 2, which included a higher proportion of patients with >3 lesions, elevated LDH, and liver and/or brain metastasis. In addition, patients in Cohort 4 received nearly twice the cumulative duration of prior anti-PD-1/PD-L1 therapy."* Given the differences in baseline characteristics, potential differences in prognosis and treatment response, please comment on the appropriateness of pooling Cohorts 2 and 4, potential biases and validity of the pooled results.

Response: Pooling efficacy and safety from Cohort 2 and 4 improves the sample size and therefore increases the precision in the point estimates of efficacy (ORR and DOR) as well as allowing for better characterization of the lifileucel safety profile. Pooling is appropriate as:

- Both cohorts used the same eligibility criteria.
- The primary objective and secondary objectives are the same for both cohorts.
- Both cohorts evaluated the efficacy of lifileucel using the ORR, as assessed by an IRC per RECIST v1.1.
- Lastly, the investigational product used in both cohorts, was manufactured using the same Generation 2 manufacturing process and specification.

Although there are differences in tumour burden and duration on prior anti-PD-1/PD-L1 therapy between patients enrolled in Cohort 2 and those enrolled in Cohort 4, the baseline disease characteristics in each cohort and when pooled together represent

broader setting of the real-world melanoma patient population in the corresponding treatment-lines.

A20. CS, Section 2.6.3, page 48. With respect to the estimated objective response rate (ORR), the CS states that *"Given the concordance between the PDAwCS efficacy set and when assessed by IRC, it is assumed results between the efficacy sets will be similar when assessed by Investigator."* Why was this assumed rather than tested in the Pooled Data Aligned with Commercial Specifications (PDAwCS) dataset? If possible, please provide the ORR for the PDAwCS efficacy set as has been done for the Full Analysis Set (FAS) in CS Table 16.

Response: In the PDAwCS, overall, there were [redacted] patients responding to treatment, which translates to [redacted] ORR within this population. This point estimate is not only a few percent away from the ORR measured in FAS, which is [redacted]; but also lies within the 95% CI of the estimated ORR in FAS; which is ([redacted]). These imply statistical closeness and indistinguishability of the response outcomes between two data sets. As these additional ORR results are not published, the company wants to keep its rights to redact this additional information.

A21. PRIORITY. CS, Section 2.6, pages 45-56 and Section 2.11.2, page 88. This section reports Kaplan-Meier (KM) plots for progression-free survival (PFS) and overall survival (OS) for the PDAwCS analysis set (i.e., people who received a within-specification lifileucel infusion). Please provide KM plots for PFS and OS for people in Cohorts 2 and 4 who did not receive the infusion (the 24 patients referred to on page 88 of the CS).

Response: Creating these plots would require additional processing of patient-level data, internal reviews and obtaining additional internal approvals before they are shared with external parties. Therefore, unfortunately, the Company will not be able provide these plots feasible within the timeframe provided for the clarification questions.

A22. CS, Section 2.11.3, page 89. The CS states that *"Although lifileucel is administered as a part of treatment regimen, the SAEs are much lower when looking at lifileucel-related AEs only. Low SAEs related to lifileucel only ([redacted]) suggest lifileucel is well-tolerated"* In contrast, the FDA clinical review (https://www.fda.gov/vaccines-

blood-biologics/approved-blood-products/amtagvi) states that *"FDA assessed the contribution of the lifileucel regimen (NMA-LD, lifileucel, and IL-2) as one entity for severe and fatal adverse events given that the Applicant has no clinical data to demonstrate the contribution of individual components of the lifileucel regimen to the overall safety."* Please comment on how the data in Section 2.11.3 should be interpreted.

Response: Lifileucel is only administered as a regimen alongside NMA-LD and IL-2. Section 2.11.3 and Table 27 shows the AE summary for both (1) AEs attributable to the whole treatment regimen, and (2) AEs attributable to lifileucel-only. This provides transparency as to the safety profile for the regimen as a whole, vs the drug only. The cost effectiveness modelling in this submission utilizes data representing the safety profile for the entire regimen.

Indirect Treatment Comparisons (ITCs)

A23. CS Section 1.3.8.1, Figure 3, page 25 and Section 2.10.3, page 67. Please comment on how including BRAF mutation-positive and patients who received more than one prior line of therapy in the simulated treatment comparison (STC) aligns with the proposed positioning of lifileucel as a second-line (2L) therapy option, as shown in CS, Figure 3.

Response: The proposed positioning of lifileucel is second-line and beyond depending on BRAF-status, which aligns to the anticipated license authorisation and to the inclusion criteria of C-144-01 (i.e. 2L+ for BRAF-wild type and 3L+ for BRAF mutation-positive).

The Company acknowledges that da Silva *et al.* 2021 (DOI: 10.1016/S1470-2045(21)00097-8), used to inform ipilimumab effectiveness data in the STC, did not include inclusion/exclusion criteria based on BRAF mutation status and may include some BRAF mutation-positive patients treated at 2L. However, it is inferred that ESMO/NCCN treatment guidelines would have been followed for treatment centres in da Silva et al. 2021, meaning a similar proportion of patients in the da Silva et al. 2021 paper would have received a prior BRAF+/-MEK inhibitor to patients in those in C-144-01. Note, 21% of ipilimumab patients were BRAF mutation-positive, which is similar to the [redacted]% in the N=[redacted] PDAwCS efficacy set.

As such, it is likely that the patients in da Silva et al. 2021 are aligned to the proposed positioning of lifileucel, in regarding to BRAF mutation status and receiving prior BRAF+/-MEK inhibitor.

For chemotherapy, Mangin *et al.* 2021 (DOI: 10.1002/cam4.3760) did not include any BRAF-mutation positive patients. Given all patients in the dataset were at 2L, the patient population criteria fully aligns with the proposed positioning of lifileucel at 2L+.

A24. PRIORITY. Company's advisory board meeting minutes (CS, reference #16), page 6. The advisory board meeting minutes indicate that the clinicians consulted mentioned a study reported by VanderWalde *et al.* (*Nature Medicine*, 2023, Vol. 29[9]) as a potential source of data for ipilimumab monotherapy for use in the STC. This study is not mentioned in the main CS. Please comment on the suitability of this study for inclusion in the STC.

Response: Whilst the VanderWalde *et al.* 2023 (DOI: 10.1038/s41591-023-02498-y) study was initially considered for the inclusion in the STC, it was deemed unsuitable due to its small sample size (N=23), which is not sufficient to inform a robust unanchored analysis. The limited sample size also means without a high level of overlap in baseline characteristics between the VanderWalde *et al.* 2023 (DOI: 10.1038/s41591-023-02498-y) population and the lifileucel PDAwCS efficacy set population, the STC would not be a robust analysis.

Furthermore, the Company maintains that da Silva *et al.* 2021 (DOI: 10.1016/S1470-2045(21)00097-8) is the most appropriate source for informing ipilimumab clinical effectiveness data in the STC versus lifileucel, as per the reasons outlined in CS Section 2.10.1, page 61: alignment of the study design and patient baseline characteristics with C-144-01. Clinicians consulted during the UK clinical advisory board meeting also confirmed da Silva *et al.* 2021 (DOI: 10.1016/S1470-2045(21)00097-8) as a suitable dataset, specifically highlighting its relevance in capturing patient characteristics and outcomes for individuals receiving ipilimumab for pretreated advanced melanoma in the UK.

A25. PRIORITY. CS, Section 2.10, page 57. Schadendorf *et al.* (Journal of Clinical Oncology, 2015, Vol. 33[17]) have reported a pooled analysis of long-term survival

data from Phase II and III trials of ipilimumab. This study reports on long-term OS for previously treated patients with metastatic melanoma who received ipilimumab. PFS data are not reported. Please clarify why this study was not considered for inclusion in the ITC (for OS).

Response: Schadendorf *et al.* 2015 (DOI: 10.1200/JCO.2014.56.2736) conducted pooled long-term OS analyses including a sample of 1,257 pre-treated patients receiving ipilimumab. However, the Company did not consider this study appropriate to inform ipilimumab clinical effectiveness data in the ITC due to the following reasons:

- **Lack of PD-1s in prior line of therapy**: The treatments patients received prior to ipilimumab administration were not specified, as this study was published prior to the full introduction of PD-1s in melanoma. Therefore, it is unclear whether the patient inclusion criteria used in the studies that informed the pooled analysis are comparable to the lifileucel population. The absence of prior systemic treatment with a PD-1 blocking antibody prior to receiving ipilimumab severely limits the eligibility of this study for the ITC inclusion, given that the proposed indication for lifileucel is for patients previously treated with PD-1 inhibitors.
- **Lack of baseline characteristics**: The studies that informed the pooled analysis did not report the pooled baseline characteristics of 2L patients receiving ipilimumab. Therefore, this study does not provide sufficient information to inform an adjusted STC.
- **Lack of PFS data**: The study did not present PFS KM plots for patients receiving ipilimumab. Given that PFS is one of the key efficacy outcomes of interest for the ITC, the lack of PFS KM data means that only OS could be used from this study to inform the ipilimumab effectiveness data for the STC.
- **Timeframe:** Some of the studies that informed the pooled analysis may not be reflective of the current clinical management standards given the time since publication (e.g., O'Day *et al.* 2010 [CA184-008, DOI: 10.1093/annonc/mdq013], Weber *et al.* 2009 [CA184-007, DOI: 10.1200/jco.2009.27.15_suppl.9033]).
- **Dose variability:** The studies that informed the pooled analysis, included doses of ipilimumab, which were not aligned with the indicated treatment dose

of ipilimumab in the UK, of 3mg/kg per administration every three weeks for a total of four doses. These studies include: CA184-024 (DOI: 10.1200/JCO.2014.56.6018), CA184-008 (DOI: 10.1093/annonc/mdq013), CA184-007 (DOI: 10.1200/jco.2009.27.15_suppl.9033), and CA184-042 (DOI: 10.1200/JCO.2014.56.2736) which used 10 mg/kg per administration.

These limitations introduce potential bias and limit the feasibility of the Schadendorf *et al.* 2015 (DOI: 10.1200/JCO.2014.56.2736) data to be used in the ITC. The Company maintains that da Silva *et al.* 2021 (DOI: 10.1016/S1470-2045(21)00097-8) is the most appropriate source for informing ipilimumab clinical effectiveness in the STC versus lifileucel, as per reasons detailed in CS Section 2.10.1, page 61.

A26. PRIORITY. CS, Section 2.10, page 57. Please present a plot with all the available KM curves from the different comparator studies: Cybulska-Stopa *et al.* (2020), da Silva *et al.* (2021), Long *et al.* (2022), Rohaan *et al.* (2022), Wilson *et al.* (2021), VanderWalde *et al.* (2023), and Schadendorf *et al.* (2015); for PFS and OS separately. Please also provide the digitised data for these curves.

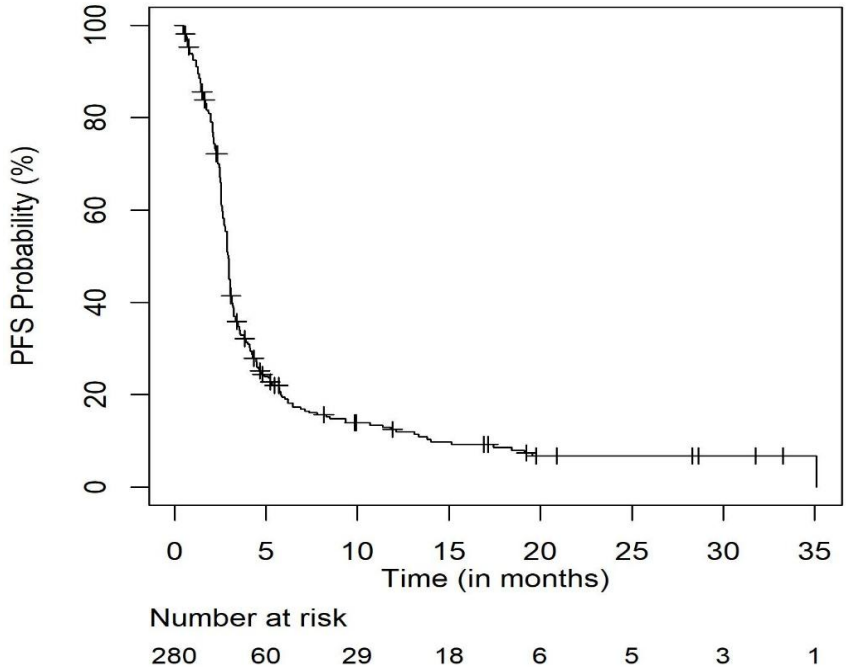
Response: Among the aforementioned publications, with the exception of Wilson *et al.* (2021), all studies reported OS data. Of these, Cybulska-Stopa *et al* (2020) reported OS data with respect to BRAF-status. In the digitization process for this study, KM curves for OS were digitized separately for each subgroup with respect to BRAF-status and then pooled together.

Regarding PFS data, Long *et al.* 2022 (DOI: 10.1016/j.annonc.2021.10.010) , Cybulska-Stopa *et al.* 2020 (DOI: 10.1016/j.advms.2020.05.005) and Schadendorf *et al.* 2015 (DOI: 10.1200/JCO.2014.56.2736) did not report KM curve for PFS.

The KM-curves generated after pooling the available PFS and OS data from the listed publications are presented in Figure 1 to Figure 3 below. Of note, the subject population in Schadendorf *et al.* 2015 (DOI: 10.1200/JCO.2014.56.2736) study was not previously treated with prior immunotherapy agents and larger than the subject populations of other studies. Therefore, below, to highlight potential outlier effects of Schadendorf *et al.* 2015 (DOI: 10.1200/JCO.2014.56.2736) on the OS profile and to maintain consistency with the target population of this appraisal, there are two separate OS plots provided: one for the pooled analysis including Schadendorf *et al.*

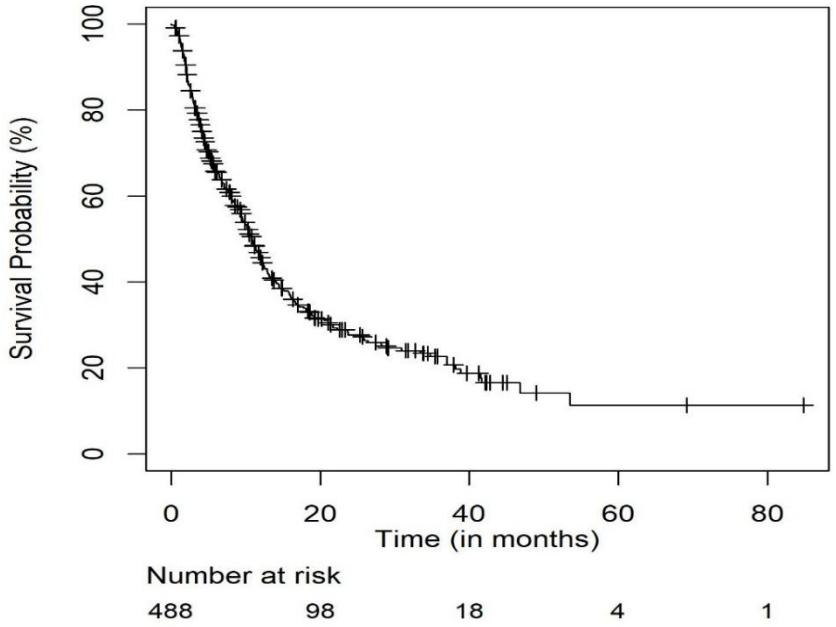
2015 (DOI: 10.1200/JCO.2014.56.2736) (Figure 3) and one for the pooled analysis excluding Schadendorf *et al.* 2015 (DOI: 10.1200/JCO.2014.56.2736) (Figure 2).

Figure 1: KM-plot for the pooled PFS Data



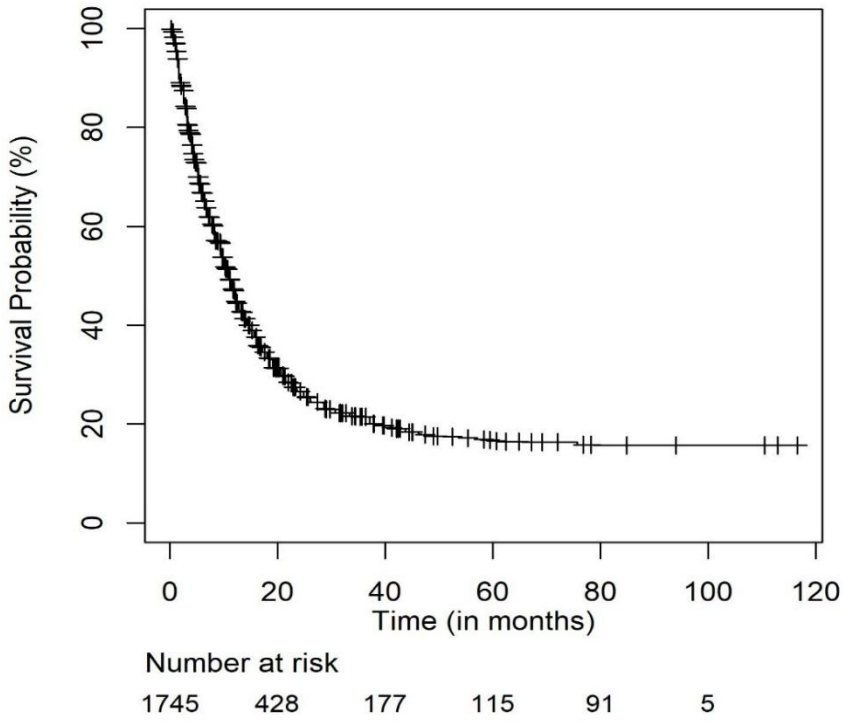
Abbreviations: KM, Kaplan-Meier; PFS, Progression-free survival.

Figure 2: KM-plot for the pooled OS Data (excluding Schadendorf *et al.* 2015)



Abbreviations: KM, Kaplan-Meier; OS, Overall survival.

Figure 3: KM-plot for the pooled OS Data (including Schadendorf *et al.* 2015)



Abbreviations: KM, Kaplan-Meier; OS, Overall survival.

A27. PRIORITY. CS, Section 2.10, page 57. For the comparison of lifileucel versus ipilimumab, please:

- Provide the code for the analysis conducted including detailed descriptions on how the survival probabilities were predicted and how hazard ratios (HRs) were calculated;
- Present the full model output of the fitted Cox regression models, including coefficients and uncertain intervals for each covariate shown in CS, Section 2.10.3, Table 23, page 71;
- Present evidence that absolute outcomes can be predicted with sufficient accuracy in relation to the relative treatment effects;
- Discuss the expected impact of failing to adjust for target lesion sum diameter and line of therapy on the results of the STC;
- Perform additional scenario analyses with a) BRAF status included; b) with BRAF status included and disease stage removed, and present the corresponding full model output, including adjusted HRs, coefficients and uncertain intervals for each covariate.

Response: The Company has provided the R code used for the STC of lifileucel versus ipilimumab for the OS outcome as “Ipilimumab OS STC code_24Apr2025”, which has been uploaded to NICE docs. The same code was applied for the PFS outcome, reading in the PFS data instead. The survival probabilities were predicted using the *predictSurvProb* function in R: *S_prob <- predictSurvProb(m_STC, newdata = comp_reconIPD_2[,covariates], times=KM_time).* This function uses timepoints from the IPD Kaplan-Meier data up to the last event that occurred, and predicts survival for the adjusted population as defined by the Cox model fit (m_STC) and the simulated covariates. Hazard ratios were calculated in the standard way with a Cox regression model.

The Company has provided the full model output of the fitted Cox regression models, including coefficients (exponential) and uncertainty (in terms of CIs) associated with each covariate in Table 1.

Table 1: Full model output of the fitted Cox regression models for the base case STC (lifileucel versus ipilimumab; PDAwCS efficacy set)

Covariate	PFS		OS	
	Exponential (coefficients)	95% CI	Exponential (coefficients)	95% CI
Age	[redacted]	[redacted]	[redacted]	[redacted]
Sex	[redacted]	[redacted]	[redacted]	[redacted]
Disease stage	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS	[redacted]	[redacted]	[redacted]	[redacted]
LDH levels	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LDH, Lactate dehydrogenase; OS, Overall survival; PDAwCS, Pooled data aligned with commercial specifications; PFS, Progression-free survival; STC, Simulated treatment comparison.

The Company acknowledges that all unanchored analyses are associated with a degree of uncertainty. However, as outlined in the CS the analysis conducted is based on the best available data and is aligned with the NICE DSU TSD18 for population adjusted comparisons. All key covariates were adjusted for in the analysis, supporting the validity of the relative treatment effect estimates used to generate absolute outcomes. Furthermore, the robustness of the analysis is demonstrated through the ‘leave-one-out’ sensitivity analyses, which showed that the STC was robust to changes in different covariates included in the model. The UK

clinical experts at the advisory board had no concerns regarding the face validity of the generated STC outputs. Given this, the Company maintains that absolute outcomes derived from the STC can be predicted with sufficient accuracy to support decision-making.

It is difficult to quantify the impact of excluding target lesion sum diameter and line of therapy from the population-adjusted STC as analyses including these covariates were not conducted given the data limitations of da Silva *et al.* 2021 (DOI: 10.1016/S1470-2045(21)00097-8). However, the selection of covariates for adjustment was guided by clinical experts consulted during the UK advisory board. The clinicians acknowledged that while the inclusion of target lesion sum diameter would be preferable, the STC had been conducted appropriately, including sufficient covariates capturing key prognostic factors and treatment effect modifiers. As such the Company maintains that the base case STC analysis is sufficient to inform the decision-making.

The Company has provided the results for the requested scenario analyses for a) BRAF status included b) with BRAF status included and disease stage removed in Table 2, while the full model outputs including the coefficients (exponential) and uncertainty (in terms of CIs) associated with each covariate are in Table 3 and Table 4. The resulting PFS and OS KM plots are provided in Figure 4 to Figure 7.

Table 2: Summary of STC scenario results (a and b) for lifileucel versus ipilimumab (PDAwCS efficacy set)

	PFS (adjusted analysis)		OS (adjusted analysis)	
	HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
CS base case adjusted analysis*	[redacted]	[redacted]	[redacted]	[redacted]
Scenario analysis a) BRAF status included	[redacted]	[redacted]	[redacted]	[redacted]
Scenario analysis b) BRAF status included and disease stage removed	[redacted]	[redacted]	[redacted]	[redacted]

* Covariates included: age, sex, disease stage, ECOG PS, High LDH levels
Abbreviations: CI, confidence interval; HR, Hazard ratio; OS, Overall survival; PDAwCS, Pooled data aligned with commercial specifications; PFS, Progression-free survival; STC, Simulated treatment comparison.

Table 3: Full model output of the fitted Cox regression models for the STC scenario analysis (a): BRAF status included (lifileucel versus ipilimumab; PDAwCS efficacy set)

Covariate	PFS		OS	
	Exponential (coefficients)	95% CI	Exponential (coefficients)	95% CI
Age	[redacted]	[redacted]	[redacted]	[redacted]
Sex	[redacted]	[redacted]	[redacted]	[redacted]
Disease stage	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS	[redacted]	[redacted]	[redacted]	[redacted]
LDH levels	[redacted]	[redacted]	[redacted]	[redacted]
BRAF status	[redacted]	[redacted]	[redacted]	[redacted]

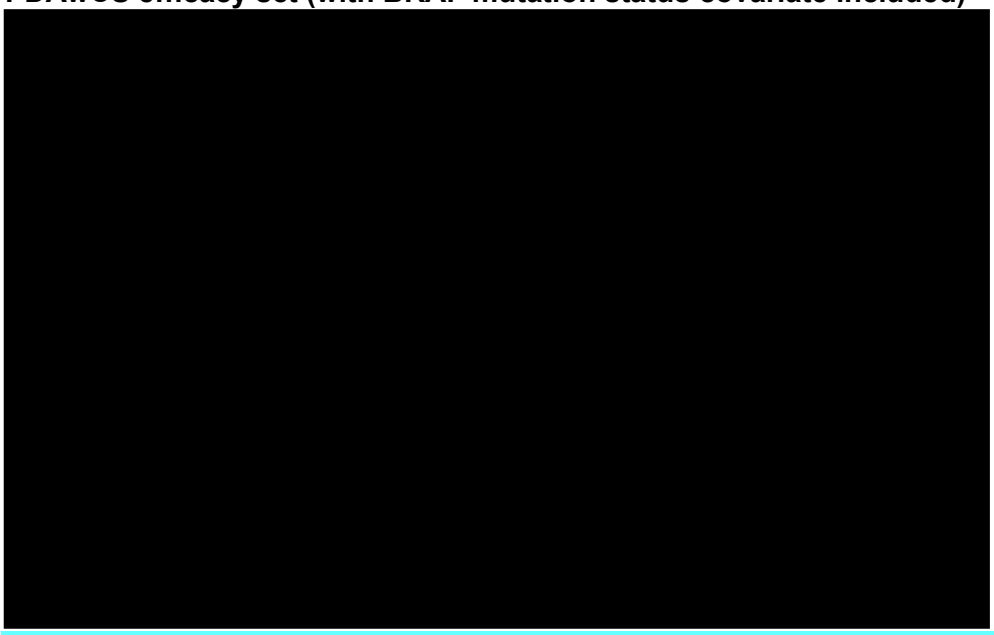
Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LDH, Lactate dehydrogenase; OS, Overall survival; PDAwCS, Pooled data aligned with commercial specifications; PFS, Progression-free survival; STC, Simulated treatment comparison.

Table 4: Full model output of the fitted Cox regression models for the STC scenario analysis (b): BRAF status included and disease stage removed (lifileucel versus ipilimumab; PDAwCS efficacy set)

Covariate	PFS		OS	
	Exponential (coefficients)	95% CI	Exponential (coefficients)	95% CI
Age	[redacted]	[redacted]	[redacted]	[redacted]
Sex	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS	[redacted]	[redacted]	[redacted]	[redacted]
LDH levels	[redacted]	[redacted]	[redacted]	[redacted]
BRAF status	[redacted]	[redacted]	[redacted]	[redacted]

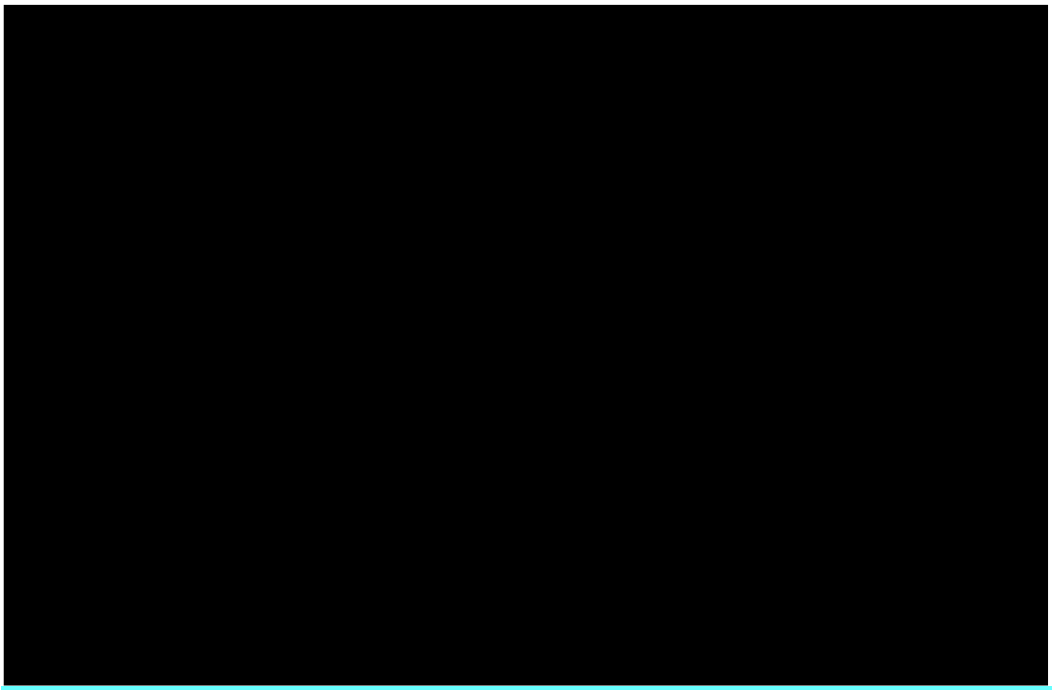
Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LDH, Lactate dehydrogenase; OS, Overall survival; PDAwCS, Pooled data aligned with commercial specifications; PFS, Progression-free survival; STC, Simulated treatment comparison.

Figure 4: Scenario a) STC KM curves of PFS of lifileucel versus ipilimumab for the PDAwCS efficacy set (with BRAF mutation status covariate included)



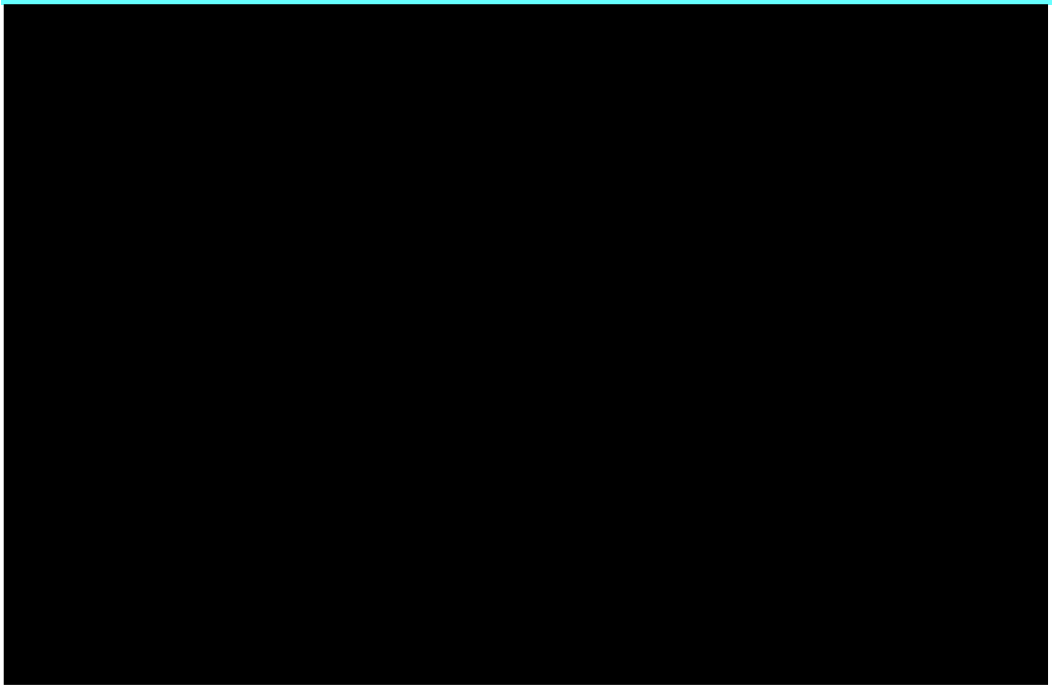
The shaded areas around each plot represent 95% confidence intervals.
Abbreviations: KM, Kaplan-Meier; PDAwCS, Pooled data aligned with commercial specifications; PFS, Progression-free survival; STC, Simulated treatment comparison.

Figure 5: Scenario a) STC KM curves of OS of lifileucel versus ipilimumab for the PDAwCS efficacy set (with BRAF mutation status covariate included)



The shaded areas around each plot represent 95% confidence intervals.
Abbreviations: KM, Kaplan-Meier; OS, Overall survival; PDAwCS, Pooled data.

Figure 6: Scenario b) STC KM curves of PFS of lifileucel versus ipilimumab for the PDAwCS efficacy set (with BRAF mutation status included and disease stage excluded)



The shaded areas around each plot represent 95% confidence intervals.

Abbreviations: KM, Kaplan-Meier; PDAwCS, Pooled data aligned with commercial specifications; PFS, Progression-free survival; STC, Simulated treatment comparison.

Figure 7: Scenario b) STC KM curves of OS of lifileucel versus ipilimumab for the PDAwCS efficacy set (with BRAF mutation status included and disease stage excluded)

The shaded areas around each plot represent 95% confidence intervals.
Abbreviations: KM, Kaplan-Meier; OS, Overall survival; PDAwCS, Pooled data

A28. CS, Section 2.10.3, Table 22, pages 69-70. Considering all patient characteristics, please clarify which population is fitter between the Study C-144-01 pooled cohorts and the da Silva *et al.* 2021 (DOI: 10.1016/S1470-2045(21)00097-8) ipilimumab group for the comparison of lifileucel versus ipilimumab.

Response: Patients in Study C-144-01 (pooled cohorts 2 and 4 [N=[redacted]]) appeared to be less fit than patients in da Silva *et al*2021 (DOI: 10.1016/S1470-2045(21)00097-8) (ipilimumab group [N=162]) based on a comparison of the key prognostic factors: age, ECOG, disease stage, LDH levels and presence of metastases, linked to patient fitness. Note patient sex was not considered in 'patient fitness'. The Company consulted with the clinical experts during the UK clinical advisory board on what the prognostic factors and treatment effect modifiers are, however, did not explicitly validate them as indicators of fitness.

On average, C-144-01 patients were younger (median [redacted] year vs. 67.0 years) and mostly had an ECOG PS of 0 ([redacted] vs. 39.5%) compared to the population in da

Silva *et al.* 2021 (DOI: 10.1016/S1470-2045(21)00097-8), meaning C-144-01 patients were less old or frail.

The staging of patients appears to be similar across datasets, when comparing the proportion of patients who were IIIC/M1a/M1b at baseline, with [redacted]% of lifileucel and 27% of ipilimumab patients. However, there were 24 patients (all from Cohort 2) who were not classified at baseline, meaning only [redacted]% of lifileucel patients were M1c/M1d, versus 73% of ipilimumab patients. Based on this, it is not possible to determine differences in patient fitness between datasets based on disease stage. See Table 5 for a comparison of disease stage for lifileucel and ipilimumab.

However, given that the majority of patients in C-144-01 had a stage IV disease ([redacted] vs. 39.5%) and around [redacted] had LDH levels above the normal range ([redacted] vs. 37.5%), as such these patients had a higher disease burden than those in da Silva *et al.* 2021 (DOI: 10.1016/S1470-2045(21)00097-8) and could be considered less fit. Patients in C-144-01 had more liver metastases, while da Silva *et al.* 2021 (DOI: 10.1016/S1470-2045(21)00097-8) population was prevalent in brain metastases. Given the balance, it is unclear which population is considered fitter in terms of metastases.

Overall, the Study C-144-01 population appeared to be less fit than da Silva *et al.* 2021 (DOI: 10.1016/S1470-2045(21)00097-8) population. This has translated into improvements in PFS and OS observed for the lifileucel population upon adjustment to the ipilimumab population through the STC (please see CS, Section 2.10.4.1, Figures 12-13).

Table 5: Comparison of disease stage at baseline for lifileucel and ipilimumab

	C-144-01 Pooled Cohorts 2 and 4 (N=[redacted])	**da Silva *et al.* 2021 (N=162)**
Stage IIIC	[redacted]	44 (27%)
Stage IV M1a	[redacted]	
Stage IV M1b	[redacted]	
Stage IV M1c	[redacted]	118 (73%)
Stage IV M1d	[redacted]	
Stage IV (not further specified)*	[redacted]	N/A

*Metastases site not collected for patients at baseline in cohort 2.

A29. CS, Section 2.10.3, Table 22, page 69-70. Considering all patient characteristics, please clarify which population is fitter between the Study C-144-01 pooled cohorts and the Mangin *et al.* 2021 immune checkpoint inhibitor (ICI) group for the comparison of lifileucel versus chemotherapy.

Response: Patients in Study C-144-01 (pooled cohorts 2 and 4 [N=[redacted]]) appeared to be slightly fitter than patients in Mangin *et al.* 2021 (DOI: 10.1002/cam4.3760) (ICI group [N=50]) based on a comparison of age, ECOG, disease stage, LDH levels and presence of metastases, all of which are linked to patient fitness.

On average, C-144-01 patients were younger than those in Mangin *et al.* 2021 (DOI: 10.1002/cam4.3760) (median [redacted] year vs. mean 68.25 years). In C-144-01, a higher proportion of patients had an ECOG PS of 0 ([redacted] vs. 39.0% [ECOG PS of 0 and 1 combined]) and lower than normal or normal levels of LDH ([redacted] vs. 23.8%), compared to patients in Mangin *et al.* 2021 (DOI: 10.1002/cam4.3760). The disease staging distribution of patients appeared to be [redacted], while a higher number of patients in Mangin *et al.* 2021 (DOI: 10.1002/cam4.3760) had brain metastases. In summary, Study C-144-01 population appeared to be fitter than Mangin *et al.* 2021 (DOI: 10.1002/cam4.3760) population.

A30. CS, Section 2.10.3, Tables 22 and 23, pages 69-71. Eastern Cooperative Oncology Group (ECOG) performance status (PS) is categorised as 0 and ≥1 for the STC but Table 22 has data for ECOG score categorised as 0, 1 or ≥2. Please clarify why the data were amalgamated and the impact that this has on the STC results.

Response: As detailed in CS, Section 2.10.3, Table 22, patients in C-144-01 had either ECOG PS of 0 ([redacted]) or 1 ([redacted]), and [redacted] had an ECOG PS of 2. In da Silva *et al.* 2021 (DOI: 10.1016/S1470-2045(21)00097-8) ipilimumab population, only 4.3% of patients (N=7) had an ECOG PS of 2. Given that there are no lifileucel patients with an ECOG PS of 2 and very few ipilimumab patients with an ECOG PS of 2, conducting a robust population-adjusted STC using ECOG PS category of 2 is not feasible. As such, the ECOG PS categories were amalgamated (0 and ≥1) to ensure validity and robustness of the analysis. The STC approach used was validated with the clinical experts during the UK clinical advisory board who did not flag any concerns.

Therefore, the Company considers that amalgamating the ECOG PS data into 0 and

≥1 categories had no impact on the robustness or validity of the STC results.

A31. CS, Section 2.10.3, Table 23, page 71. Disease stage is not classified consistently across studies in the STC; rather, it is categorised as: IIIC and IV for Study C-144-01 and III/M1a/M1b and M1c/M1d for da Silva *et al.* (2021).

- Please comment on the suitability of having **dissimilar disease stage classifications** between the two studies and the impact this has on the STC results;
- Please clarify whether disease metastasis data are available from the individual patient data (IPD) for Cohort 2 in Study C-144-01;
- Please clarify if M1c/d indicates a worse prognosis than M1a/b;
- Please present the full model output of the fitted Cox regression model dividing the lifileucel population into III/M1a/M1b and M1c/M1d using the fact that (in the worst-case scenario) only 73.6% of the pooled lifileucel population could be M1c/d at study entry (assuming that every patient with Stage IV disease in Cohort 2 has M1c/M1d).

Response: The Company acknowledge that the use of dissimilar disease stage classifications is a limitation of the STC, however, the Company maintains that the base case STC is robust and appropriate for decision making.

As outlined in the response to A28, staging at baseline was only reported by III/M1a/M1b vs. M1c/M1d in da Silva *et al.* 2021 (DOI: 10.1016/S1470-2045(21)00097-8). Additionally, the Company confirm that the staging classification by metastases was not collected at baseline for lifileucel in Cohort 2 of C-144-01, as such it is not possible to conduct an STC based on the covariate groupings of III/M1a/M1b and M1c/M1d for lifileucel, as there are 24 patients with missing M1a/b/c/d data.

The Company maintain that the approach to use lifileucel stage III vs. IV covariate data and ipilimumab III/M1a/M1b vs. M1c/M1d covariate data is an appropriate solution given the data limitations, given that the M1c/d classified patients are patients who have the worst prognosis compared to M1a/b, as summarised by the AJCC (2018, DOI: 10.1080/14737140.2018.1489246).Furthermore, the leave-one-out analysis showed that removing disease stage from the base case model did not

change the pattern of significance in the relative treatment effects and yielded comparable point estimates both for PFS and OS endpoints. Based on this the Company maintains that the base case STC is robust and appropriate for decision making.

The Company has conducted survival analysis by disease stage groupings in the lifileucel population, by Stage III/M1a/M1b (N=[redacted]) and M1c/M1d (N=[redacted]) (assuming that every patient with Stage IV disease in Cohort 2 has M1c/M1d). See Table 6 presenting the outputs of the Cox model and

Figure 8 to

Figure 11 presenting the Kaplan Meier plots.

Table 6: Summary of non-parametric PFS and OS outputs for C-144-01 patients stratified by Stage III/M1a/b (N=[redacted]) and Stage IIIV M1c/b (N=[redacted])

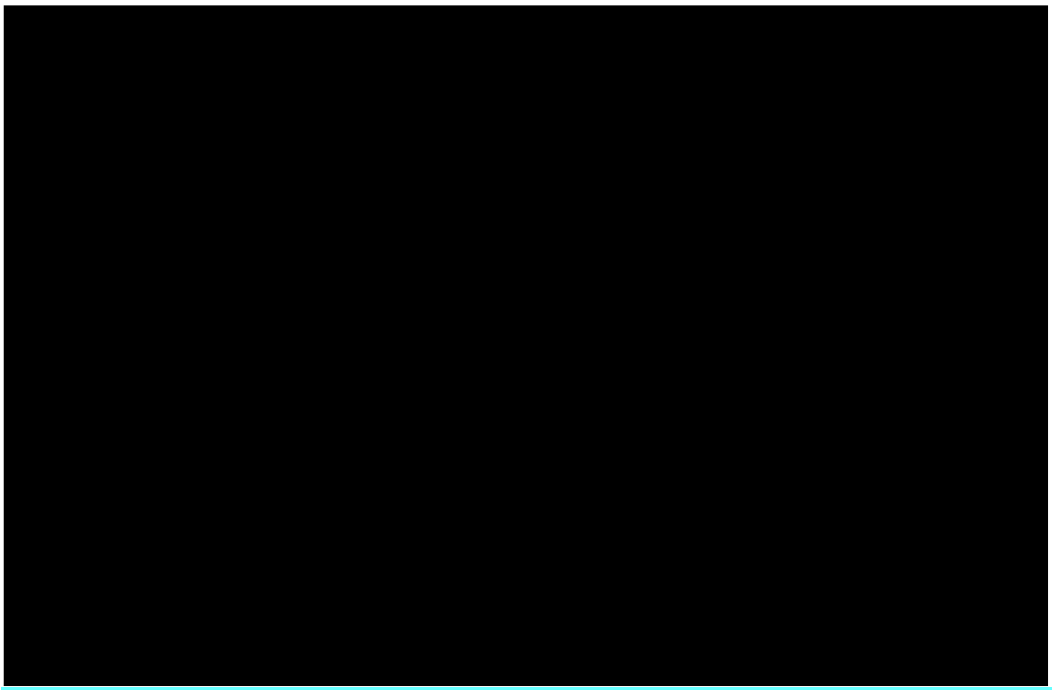
	PFS		OS	
	Median (95% CI)	**Events**	**Median (95% CI)**	**Events**
Stage III/M1a/b (N=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Stage IV M1c/b (N=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence intervals; PFS, progression-free survival; OS, overall survival

Figure 8: PFS KM curve for the lifileucel Stage III/M1a/M1b population (PDAwCS efficacy set) (N=[redacted])

The shaded areas around each plot represent 95% confidence intervals.
Abbreviations: Abbreviations: KM, Kaplan-Meier; PDAwCS, Pooled data aligned with commercial specifications; PFS, Progression-free survival; STC, Simulated treatment comparison.

Figure 9: OS KM curve for the lifileucel Stage III/M1a/M1b population (PDAwCS efficacy set) (N=[redacted])



The shaded areas around each plot represent 95% confidence intervals.
Abbreviations: Abbreviations: KM, Kaplan-Meier; OS, Overall survival; PDAwCS, Pooled data aligned with commercial specifications; STC, Simulated treatment comparison.

Figure 10: PFS KM curve for the lifileucel M1c/M1d population (PDAwCS efficacy set) (N=[redacted])

The shaded areas around each plot represent 95% confidence intervals.
Abbreviations: Abbreviations: KM, Kaplan-Meier; PDAwCS, Pooled data aligned with commercial specifications; PFS, Progression-free survival; STC, Simulated treatment comparison.

Figure 11: OS KM curve for the lifileucel M1c/M1d population (PDAwCS efficacy set) (N=[redacted])

The shaded areas around each plot represent 95% confidence intervals.
Abbreviations: Abbreviations: KM, Kaplan-Meier; OS, Overall survival; PDAwCS, Pooled data aligned with commercial specifications; STC, Simulated treatment comparison.

A32. PRIORITY. CS, Section 2.10, page 57. For both PFS and OS, please provide a matching adjusted indirect comparison (MAIC) analysis for the comparison of lifileucel versus ipilimumab with appropriate covariates adjusted. Please present the full analysis results including adjusted HRs, adjusted KM curves, weight distributions and effective sample size. The EAG acknowledges that a MAIC suffers from a large reduction in effective sample size when the covariate overlapping is poor, but considers that such an analysis would provide further justification to the ITC results.

Response: The Company does not consider performing a MAIC analysis feasible within the timeframe for the clarification questions response. An unanchored population-adjusted STC was selected as more appropriate for decision-making than a MAIC approach as detailed in the CS Section 2.10.2, pages 65-66. In summary, the key factor that contributed to selection of STC over MAIC was the extent of overlap in baseline characteristics of the populations, and there was evidence that STC perform better where there is lower overlap between the populations . Given this, the Company have not presented a MAIC in response to this clarification

question.

A33. CS, Section 2.10.1, page 61. The CS states *"Using a sample as small as 50 patients means that the comparison places reliance on a small number of data, resulting in uncertainty in the analysis outputs. Therefore, given this limitation, it was not feasible to use Mangin et al. (2021) in a population-adjusted indirect comparison versus lifileucel."* Please explain why the small sample size in Mangin *et al.* should preclude the use of population adjustment using this source.

Response: Conducting a population-adjusted indirect comparison using a sample size as small as 50 patients would result in low statistical power, limiting the ability to accurately detect true differences in outcomes between interventions or adequately adjust for prognostic factors and effect modifiers. Moreover, a small sample may not provide an appropriate representation of covariate distributions required in population adjustment, hence, the adjustments may be based on unrepresentative data. These limitations increase the uncertainty of treatment effect estimates and introduce potential bias, reducing the robustness and generalisability of the population-adjusted results. Therefore, the Company maintains that it is not feasible to perform a robust population-adjusted STC for chemotherapy versus lifileucel using Mangin *et al.* 2021 (DOI: 10.1002/cam4.3760), and instead a naïve unadjusted comparison was presented (see CS page 76).

A34. CS, Section 3.3.1.5, pages 145 and 156, and company's advisory board meeting minutes (CS reference #16), page 7. The company's model applies an HR of 2.0 to the chemotherapy group to derive PFS and OS estimates for BSC. However, the company's advisory board meeting minutes state that *"Some KOLs said that chemotherapy was about the same as giving no treatment."* Please clarify how many clinical experts shared this view and explain why the economic model does not apply an HR of 1.0 for BSC versus chemotherapy.

Response: As mentioned in Section 3.3.1.1 of the CS, Mangin *et al.* 2021 (DOI: 10.1002/cam4.3760) was used as a proxy for BSC efficacy due to the lack of available data sources. While *"some KOLs said that chemotherapy was about the same as giving no treatment"*, there was a broad agreement that BSC was meaningfully inferior to chemotherapy in terms of both survival and progression outcomes. The KOLs agreed "*that BSC was significantly inferior to chemotherapy,*

and structured elicitation resulted in agreement that it could be represented by a curve that was 50% worse than the chemotherapy response curve and progression curve. One KOL stated that there could be OS of 1% at 3 years, anecdotally, which supports separation between the chemotherapy and BSC curves", as recorded in the company's advisory board meeting minutes. This informed the application of an HR of 2.0 for BSC versus chemotherapy within the model, rather than assuming equivalence, to more accurately reflect the expected clinical benefit of chemotherapy over BSC.

Section B: Clarification on cost-effectiveness data

Parametric survival models

B1. PRIORITY. CS, Section 3.2.2.4, page 106. The CS states *"Additionally, a small proportion of patients on ipilimumab are expected to experience cure and consequently long-term survival."* Given that cure is expected for some patients receiving ipilimumab, why have only standard parametric survival models been fitted to the data for ipilimumab?

Response: As per the company submission (Section 3.3.1.1), the Company maintains that the MCM approach was not appropriate for ipilimumab due to limited follow-up. The OS KM curve for ipilimumab showed no flattening and the PFS KM curve for ipilimumab showed a small plateau at approximately 15 months which only lasted until approximately month 19 before decreasing thereafter (da Silva *et al.* 2021 [DOI: 10.1016/S1470-2045(21)00097-8]). This is in contrast to the long-lasting plateaus of lifileucel in the PFS KM curve, observed between approximately [redacted] until end of follow-up ([redacted]), and the OS KM curve, observed between approximately [redacted] until end of follow-up ([redacted]). Additionally, the identified literature for use of ipilimumab as a further line of treatment in melanoma suggested that the proportion of ipilimumab patients with a long-term survival was negligible (CS Section 3.3.1.4).

As mentioned in company submission (Section 3.2.2.7), in the phase 3, randomized CheckMate 067 study (DOI: 10.1056/NEJMoa2407417), there was a strong association between 3-year PFS rates and long-term survivorship rates, hence why in the base case, a 3-year PFS rate was used as a proxy for long term survival. The

follow-up for PFS data for ipilimumab did not reach the 3-year mark unlike lifileucel (follow-up of 22.1 months versus [redacted], respectively). This relatively immature follow-up along with the lack of long-lasting plateaus would have resulted in numerically unstable cure rates for ipilimumab if a MCM was run.

Based on the reasons provided above, the Company maintains the use of MCM for lifileucel only and that SPM was reflective for ipilimumab. Additionally, the modelling approaches for treatments were validated by five UK clinical experts at an advisory board (17th October 2024). However, to account for the clinical expert's expectation of a small proportion of ipilimumab patients experiencing long-term survival, it was assumed that patients who are progression free at 3-years will achieve SMR-adjusted age- and gender-specific survival of the general population. Please note the reference to cure is an error for which we apologise, the sentence should read "*Additionally, a small proportion of patients on ipilimumab are expected to experience long-term survival."*

B2. CS, Section 3.3.1.5, Table 36, page 136 and Table 45, page 147. The mixture-cure models (MCMs) selected for lifileucel (excluding the STC-adjustment) suggest that the cure fraction for OS is [redacted] higher than that for PFS. Given that patients are assumed to receive no further therapy after progression which could provide additional treatment benefits, please comment on the plausibility of applying different cure fractions for each endpoint in the economic model.

Response: As stated in the CS, page 127, under the heading *Mixture Cure Modelling Approach Concept*, it was specified that:

- The cure rates for PFS has a strict definition of 'clinical cure', where complete tumour cell eradication occurs. Once progression is observed, long-term survival is no longer achievable, and patients cannot be considered cured.
- Consequently, cured PFS patients are only susceptible to non-disease-related deaths, without the risk of progression or disease-related mortality.
- In contrast, the cure rates for OS represent a more nuanced assumption, acknowledging that some patients may still achieve long-term survival even after experiencing progression. This perspective allows for the possibility of delayed treatment effects influencing patient outcomes.

Given these distinct definitions and assumptions, it is reasonable to expect differences in cure rates derived from MCM. These assumptions also aligned with NICE TA975 (https://www.nice.org.uk/guidance/ta975) where the company's base case MCM suggested different cure fractions for each endpoint in the economic model (cure fractions of 34.9% for EFS and 42.4% for OS in the tisagenlecleucel group).

B3. PRIORITY. CS, Section 3.3.1.5, Table 36, page 136 and Table 45, page 147. The MCMs fitted to the unadjusted data Study C-144-01 indicate cure fractions for lifileucel of [redacted] for PFS and [redacted] for OS. These estimates are broadly consistent with clinical advice from experts who attended the advisory board meeting (expected cure [redacted]). However, the STC-adjusted MCMs for lifileucel imply much higher cure fractions for PFS and OS, with plateaus occurring at around [redacted] and [redacted] respectively. Given that the STC-adjusted MCMs for lifileucel are not in line with clinical input received and do not relate to the target population for lifileucel, please comment on why these models should be considered meaningful for decision-making.

Response: As explained in the answer to A28, the lifileucel patients in Study C-144-01 appeared to be less fit than ipilimumab patients in da Silva *et al.* 2021 (DOI: 10.1016/S1470-2045(21)00097-8). This has translated into improvements in PFS and OS for the lifileucel population when adjusting to the ipilimumab population and is reflected in the higher cure fractions. The expected cure fractions suggested by the clinical experts are reflective of patients with baseline characteristics as in lifileucel Study C-144-01 but not the patients with baseline characteristics in da Silva *et al.* 2021 (DOI: 10.1016/S1470-2045(21)00097-8), hence the discrepancy. The Company acknowledges the limitations in the data, as described in the CS Section 2.13 and 3.14.However, the company considers that it is crucial to account for differences between populations included in the Study C-144-01 and da Silva *et al.* 2021 (DOI: 10.1016/S1470-2045(21)00097-8) to allow for a fair comparison of these two interventions and maintains that methods utilised are the most robust.

B4. PRIORITY. CS, Section 3.3.1.5, Figure 20, page 138, and Figure 26, page 149. The plots in Figures 20 and 26 show the smoothed empirical hazard and the model-predicted hazard for the log-logistic MCM for PFS for lifileucel and for the exponential

MCM for OS for lifileucel. Please amend each plot to also show the model-predicted hazard for the other MCMs for PFS or OS not included in the base case model.

Response: The company has provided figures below that compare the observed and predicted PFS and OS hazards for different parametric distribution MCMs alongside general population OS hazards. The generalised gamma MCM for PFS was not included as convergence was not achieved.

The company acknowledges a small error in labelling in the company submission Section 3.3.1.5, Figure 20, page 138. The caption says log-logistic but it should be log-normal.

PFS hazards

Figure 12: Comparison of the observed and predicted PFS hazards for lifileucel exponential MCM alongside general population OS hazards

Abbreviations: MCM, Mixture cure modelling; OS, Overall survival; PFS, Progression-free survival.

Figure 13: Comparison of the observed and predicted PFS hazards for lifileucel Weibull MCM alongside general population OS hazards

Abbreviations: MCM, Mixture cure modelling; OS, Overall survival; PFS, Progression-free survival.

Figure 14: Comparison of the observed and predicted PFS hazards for lifileucel Gompertz MCM alongside general population OS hazards

Abbreviations: MCM, Mixture cure modelling; OS, Overall survival; PFS, Progression-free survival.

Figure 15: Comparison of the observed and predicted PFS hazards for lifileucel log-logistic MCM alongside general population OS hazards

Abbreviations: MCM, Mixture cure modelling; OS, Overall survival; PFS, Progression-free survival.

Figure 16: Comparison of the observed and predicted PFS hazards for lifileucel log-normal MCM alongside general population OS hazards

Abbreviations: MCM, Mixture cure modelling; OS, Overall survival; PFS, Progression-free survival.

OS hazards

Figure 17: Comparison of the observed and predicted OS hazards for lifileucel exponential MCM alongside general population OS hazards

Abbreviations: MCM, Mixture cure modelling; OS, Overall survival; PFS, Progression-free survival.

Figure 18: Comparison of the observed and predicted OS hazards for lifileucel Weibull MCM alongside general population OS hazards

Abbreviations: MCM, Mixture cure modelling; OS, Overall survival.

Figure 19: Comparison of the observed and predicted OS hazards for lifileucel Gompertz MCM alongside general population OS hazards

Abbreviations: MCM, Mixture cure modelling; OS, Overall survival.

Figure 20: Comparison of the observed and predicted OS hazards for lifileucel log-logistic MCM alongside general population OS hazards

Abbreviations: MCM, Mixture cure modelling; OS, Overall survival.

Figure 21: Comparison of the observed and predicted OS hazards for lifileucel log-normal MCM alongside general population OS hazards

Abbreviations: MCM, Mixture cure modelling; OS, Overall survival.

Figure 22: Comparison of the observed and predicted OS hazards for lifileucel generalised gamma MCM alongside general population OS hazards

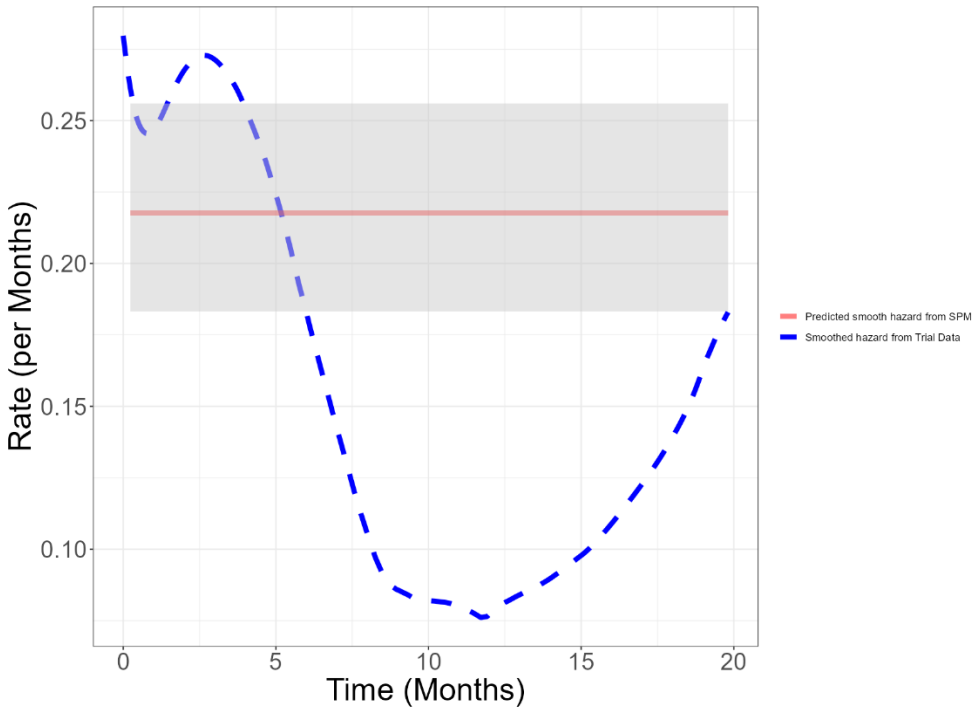
Abbreviations: MCM, Mixture cure modelling; OS, Overall survival.

B5. PRIORITY. CS, Section 3.3.1.5, pages 133-156. Please provide plots showing the empirical (smoothed) hazard and the model-predicted hazards for PFS and OS for the standard parametric models fitted to the data for the ipilimumab monotherapy and chemotherapy groups.

Response: The company has provided figures below that compare the observed and predicted PFS and OS hazards for different parametric distribution SPMs alongside general population OS hazards for ipilimumab and chemotherapy.

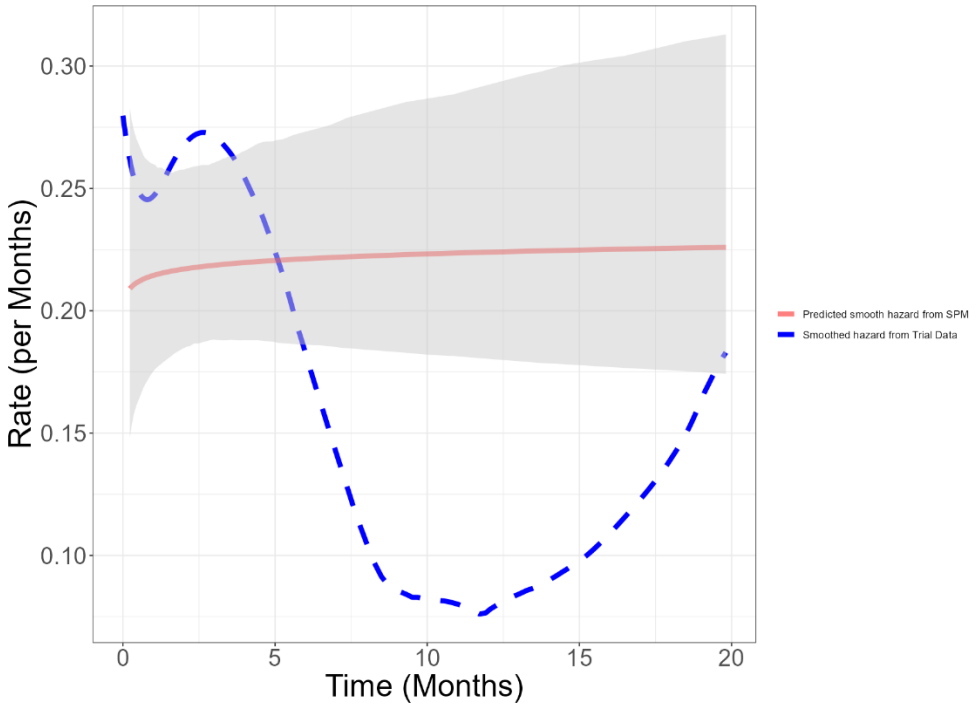
Ipilimumab - PFS hazards

Figure 23: Comparison of the observed and predicted PFS hazards for ipilimumab exponential SPM



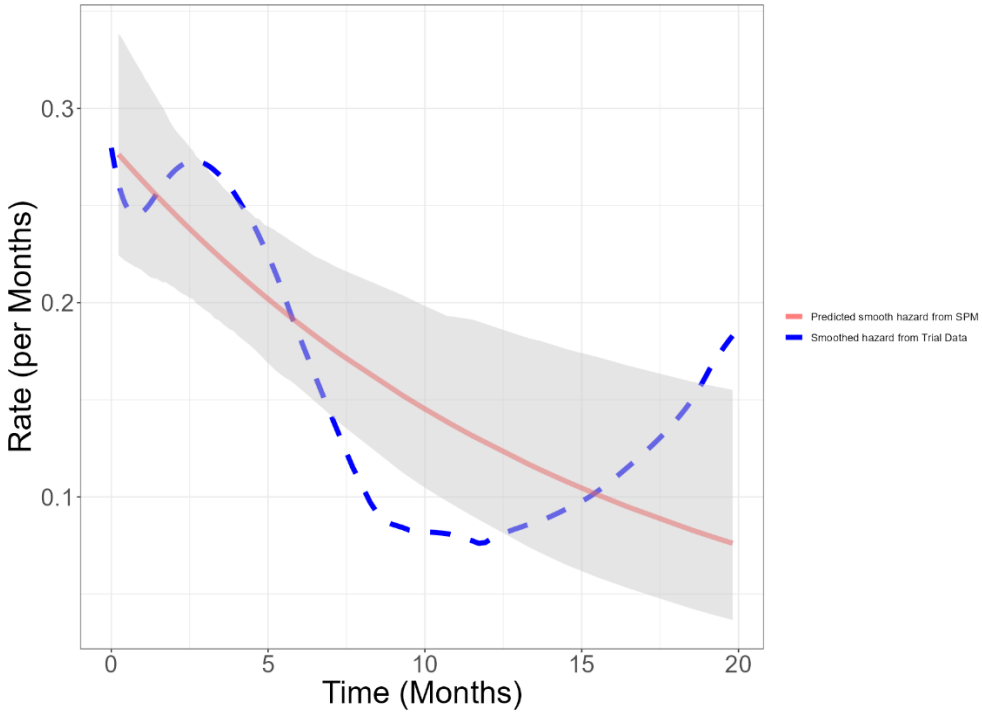
Abbreviations: PFS, Progression-free survival; SPM, Standard parametric modelling.

Figure 24: Comparison of the observed and predicted PFS hazards for ipilimumab Weibull SPM



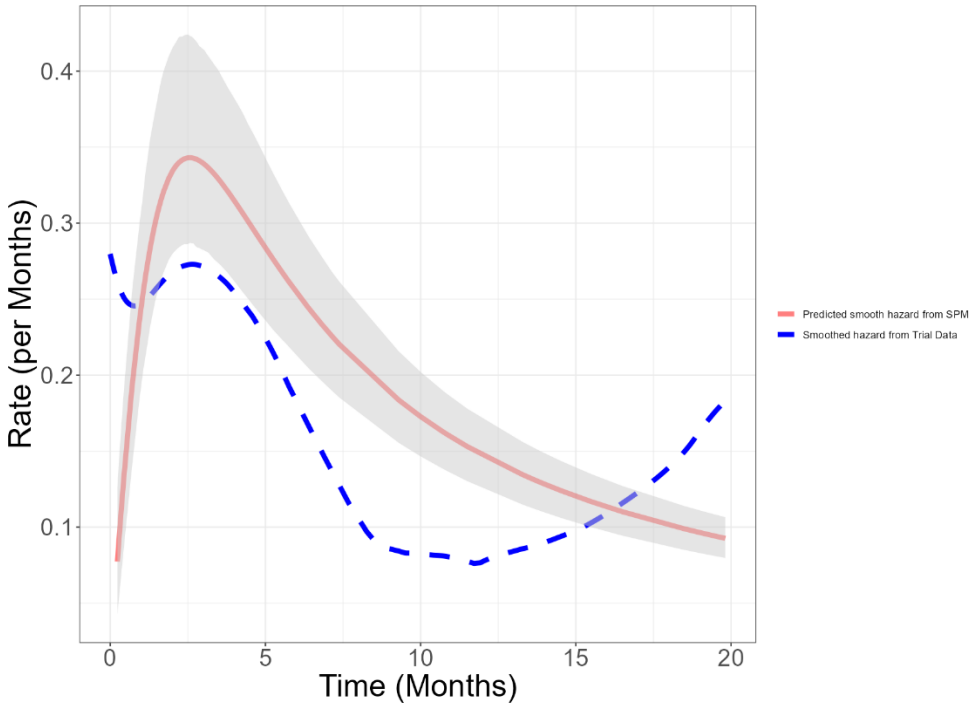
Abbreviations: PFS, Progression-free survival; SPM, Standard parametric modelling.

Figure 25: Comparison of the observed and predicted PFS hazards for ipilimumab Gompertz SPM



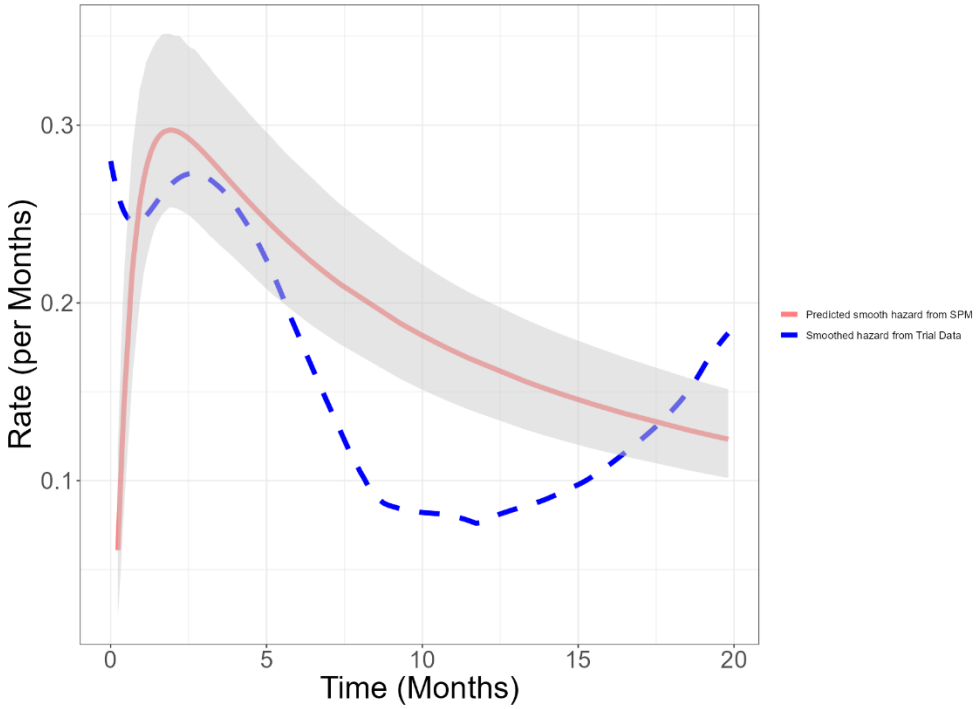
Abbreviations: PFS, Progression-free survival; SPM, Standard parametric modelling.

Figure 26: Comparison of the observed and predicted PFS hazards for ipilimumab log-logistic SPM



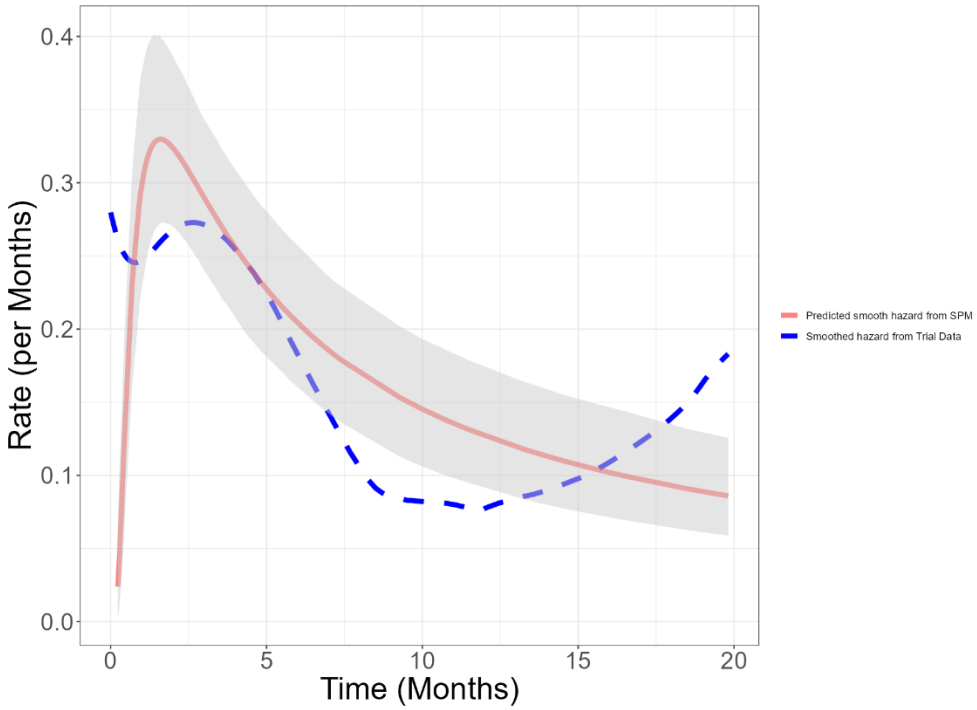
Abbreviations: PFS, Progression-free survival; SPM, Standard parametric modelling.

Figure 27: Comparison of the observed and predicted PFS hazards for ipilimumab log-normal SPM



Abbreviations: PFS, Progression-free survival; SPM, Standard parametric modelling.

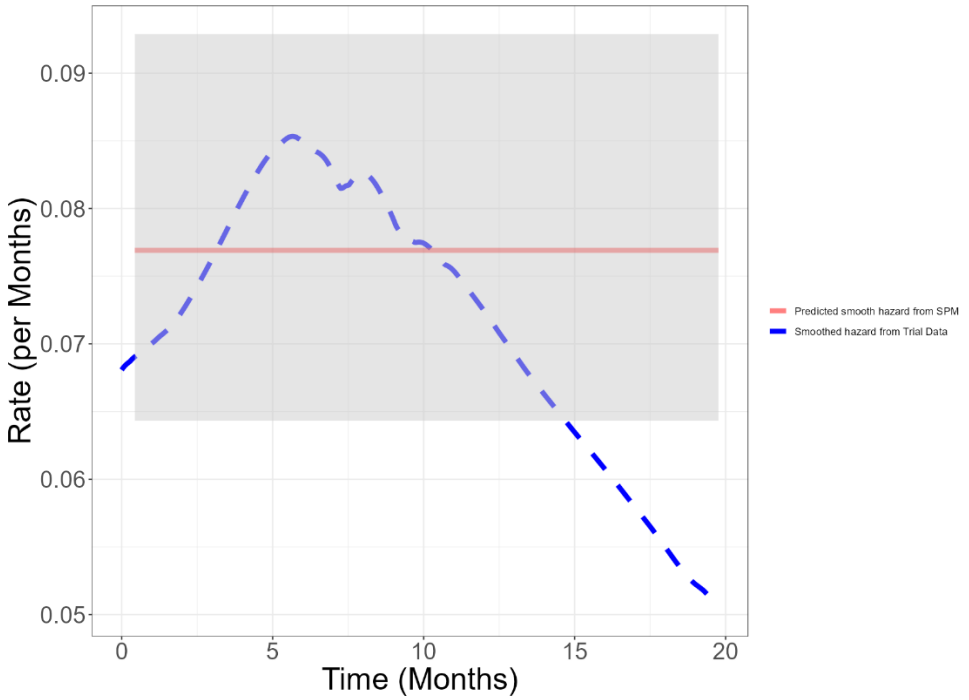
Figure 28: Comparison of the observed and predicted PFS hazards for ipilimumab generalised gamma SPM



Abbreviations: PFS, Progression-free survival; SPM, Standard parametric modelling.

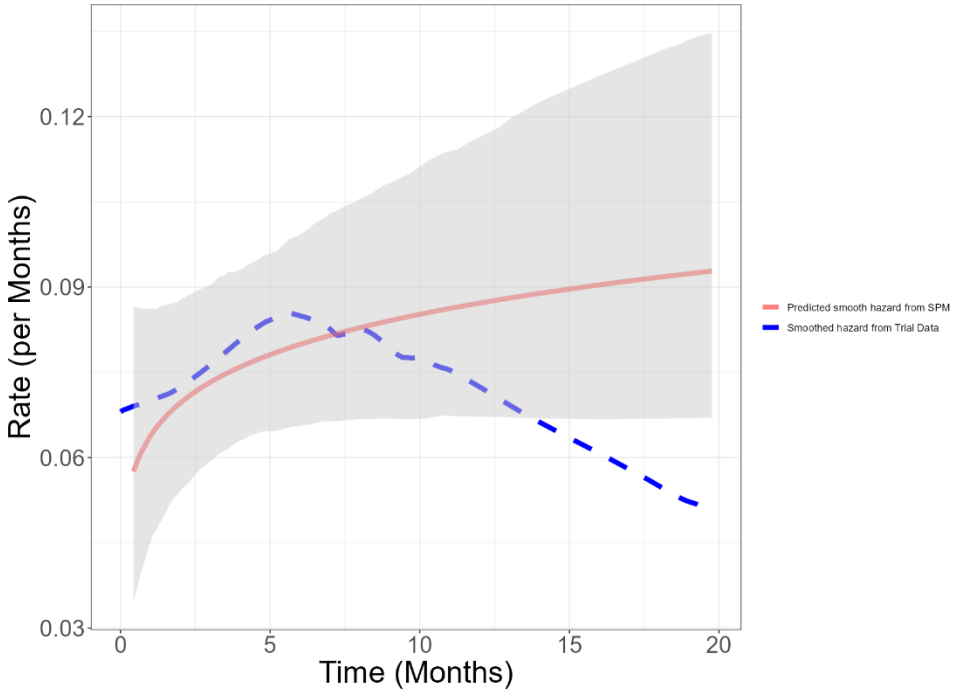
Ipilimumab - OS hazards

Figure 29: Comparison of the observed and predicted OS hazards for ipilimumab exponential SPM



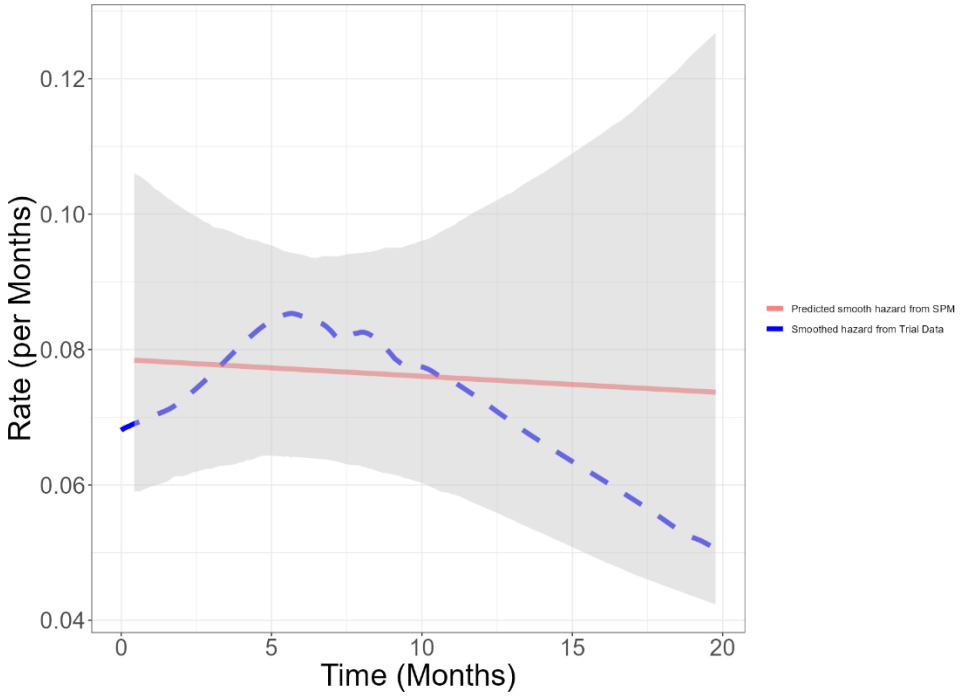
Abbreviations: OS, Overall survival; SPM, Standard parametric modelling.

Figure 30: Comparison of the observed and predicted OS hazards for ipilimumab Weibull SPM



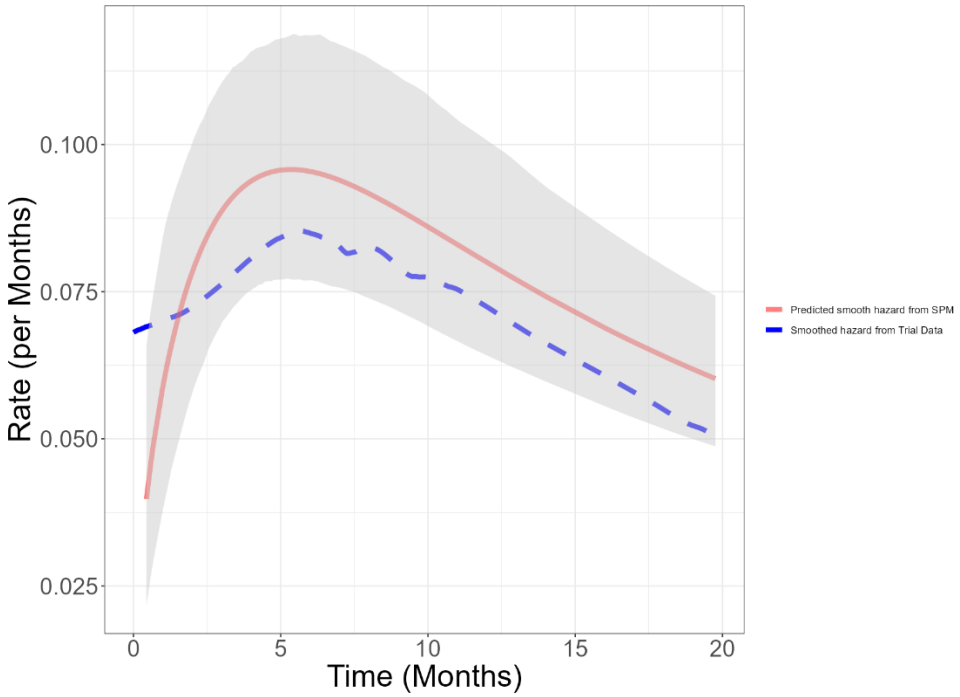
Abbreviations: OS, Overall survival; SPM, Standard parametric modelling.

Figure 31: Comparison of the observed and predicted OS hazards for ipilimumab Gompertz SPM



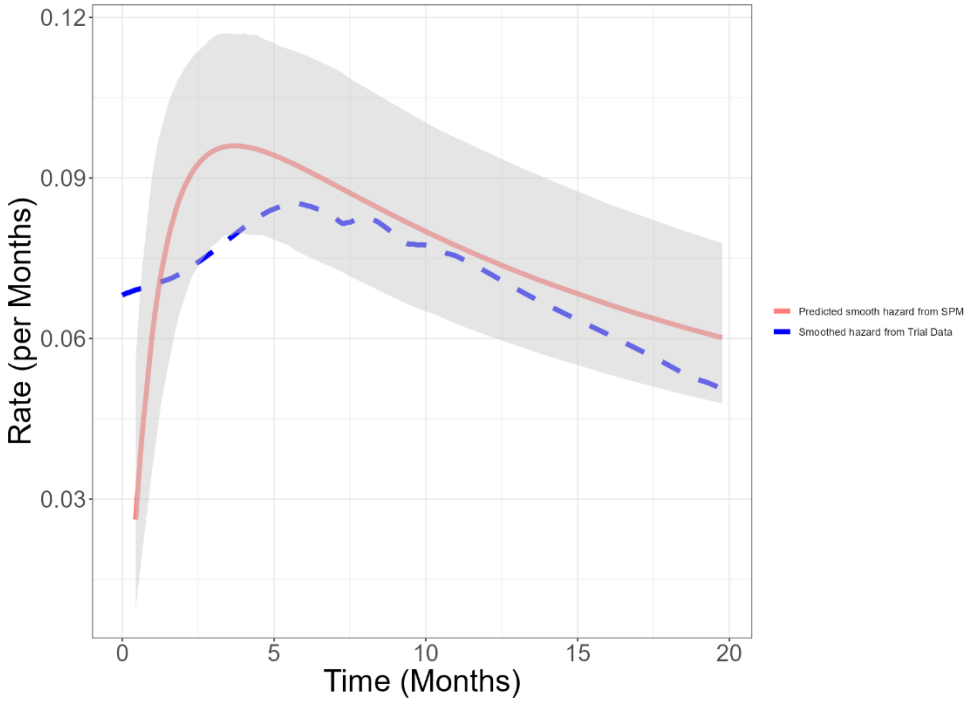
Abbreviations: OS, Overall survival; SPM, Standard parametric modelling.

Figure 32: Comparison of the observed and predicted OS hazards for ipilimumab log-logistic SPM



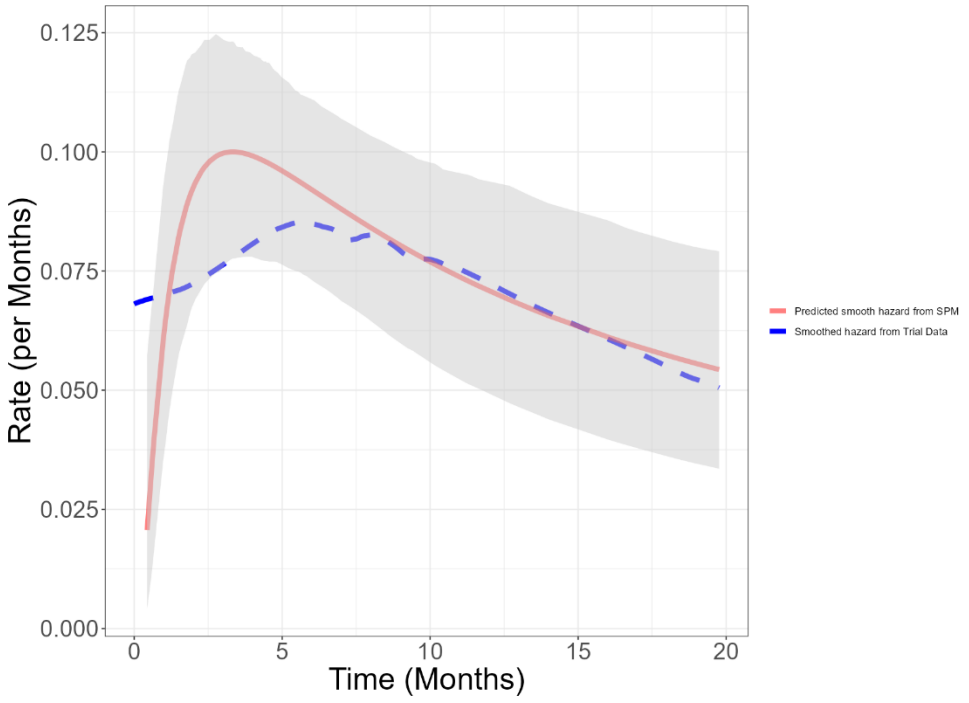
Abbreviations: OS, Overall survival; SPM, Standard parametric modelling.

Figure 33: Comparison of the observed and predicted OS hazards for ipilimumab log-normal SPM



Abbreviations: OS, Overall survival; SPM, Standard parametric modelling.

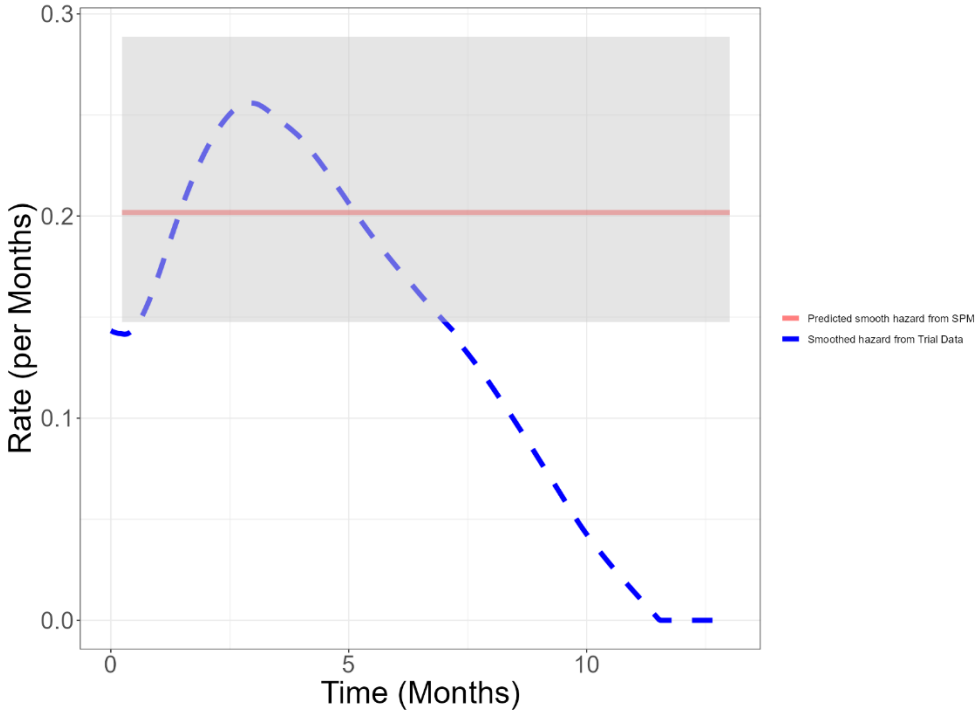
Figure 34: Comparison of the observed and predicted OS hazards for ipilimumab generalised gamma SPM



Abbreviations: OS, Overall survival; SPM, Standard parametric modelling.

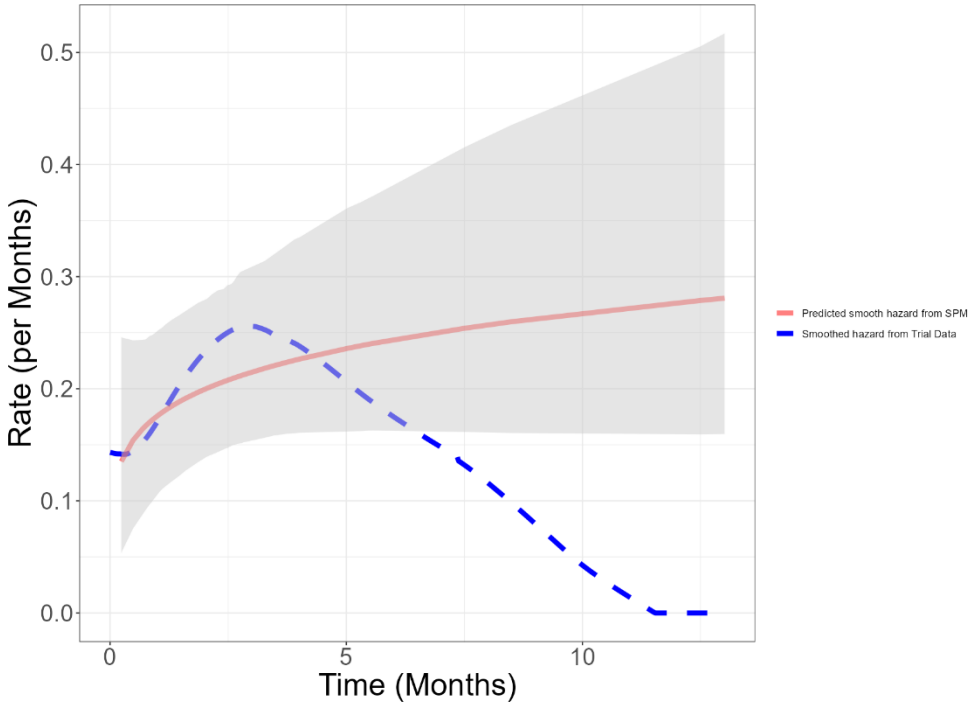
Chemotherapy - PFS hazards

Figure 35: Comparison of the observed and predicted PFS hazards for chemotherapy exponential SPM



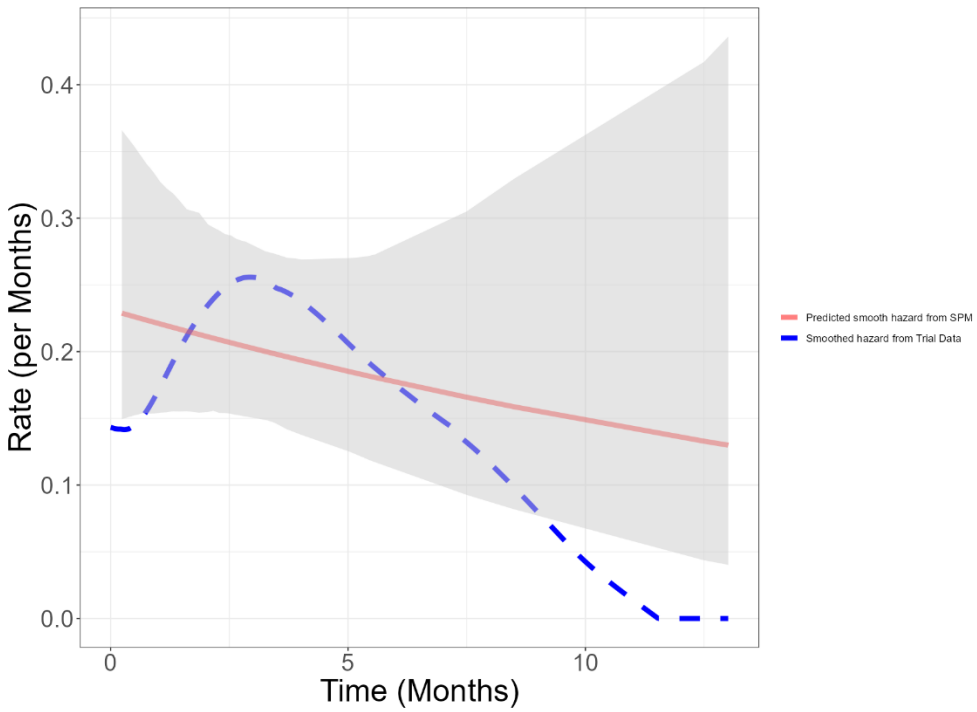
Abbreviations: PFS, Progression-free survival; SPM, Standard parametric modelling.

Figure 36: Comparison of the observed and predicted PFS hazards for chemotherapy Weibull SPM



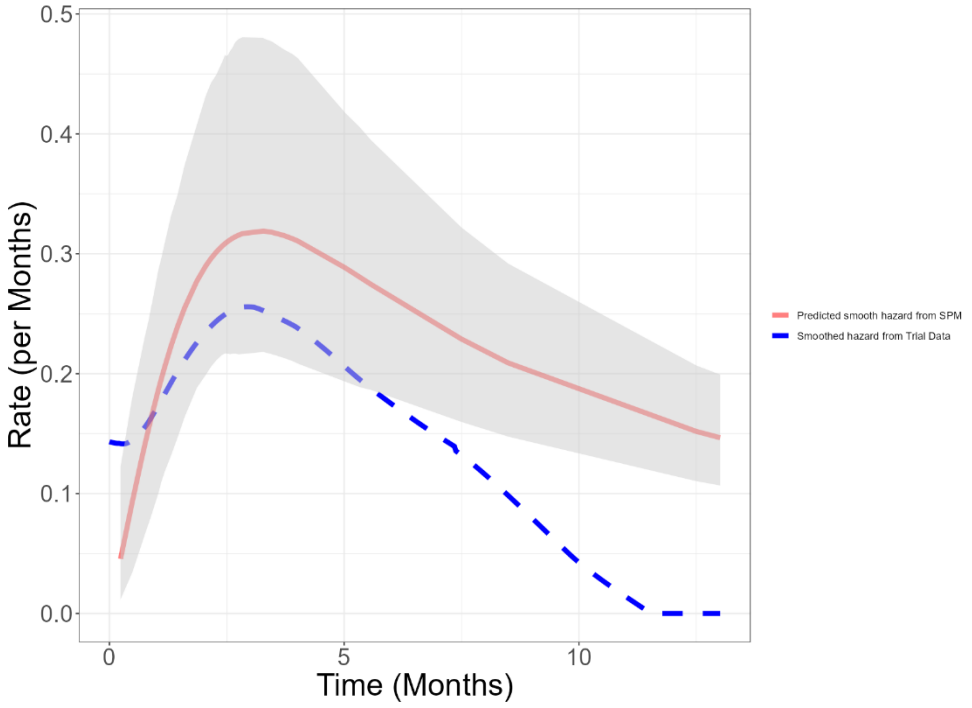
Abbreviations: PFS, Progression-free survival; SPM, Standard parametric modelling.

Figure 37: Comparison of the observed and predicted PFS hazards for chemotherapy Gompertz SPM



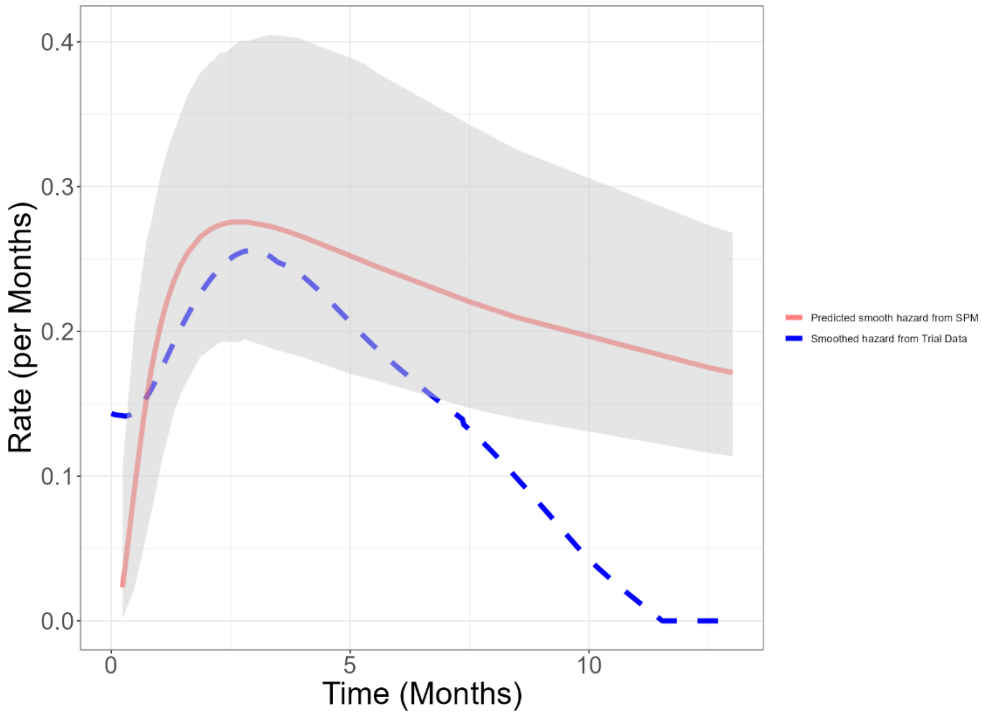
Abbreviations: PFS, Progression-free survival; SPM, Standard parametric modelling.

Figure 38: Comparison of the observed and predicted PFS hazards for chemotherapy log-logistic SPM



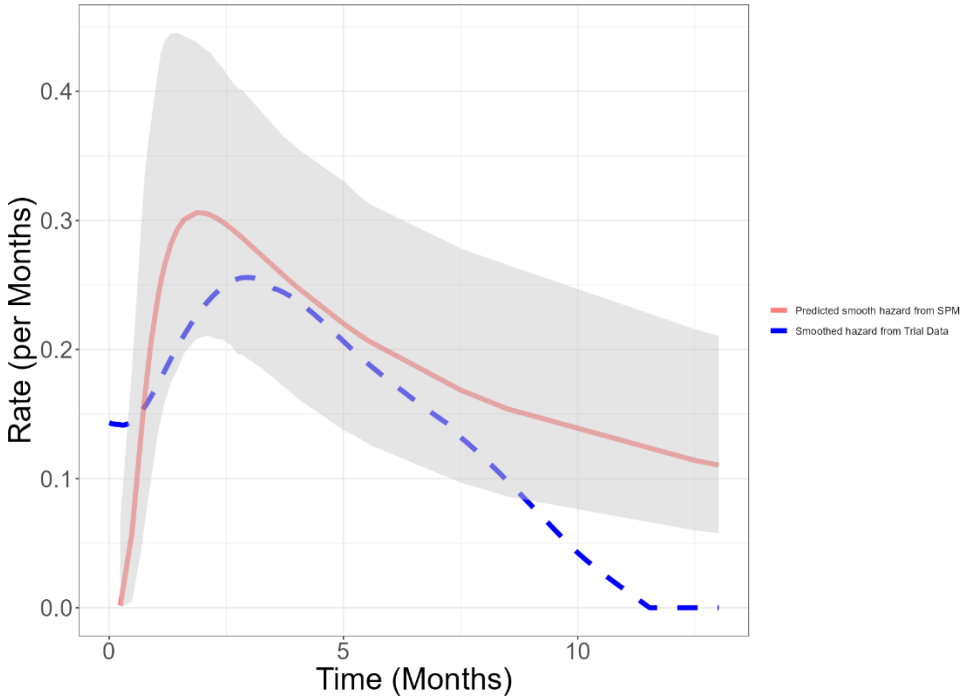
Abbreviations: PFS, Progression-free survival; SPM, Standard parametric modelling.

Figure 39: Comparison of the observed and predicted PFS hazards for chemotherapy log-normal SPM



Abbreviations: PFS, Progression-free survival; SPM, Standard parametric modelling.

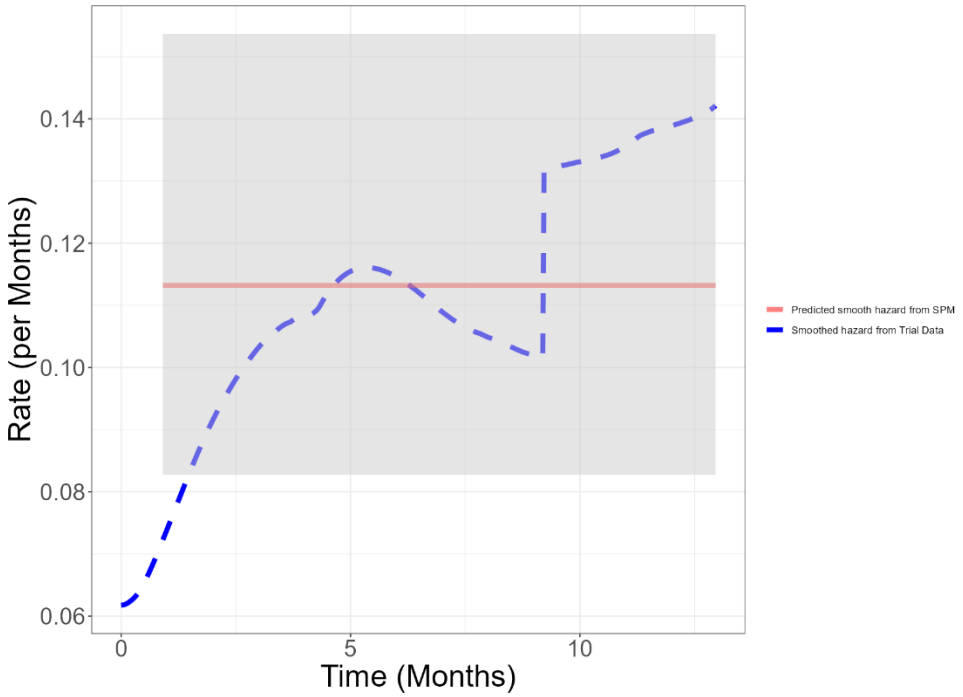
Figure 40: Comparison of the observed and predicted PFS hazards for chemotherapy generalised gamma SPM



Abbreviations: PFS, Progression-free survival; SPM, Standard parametric modelling.

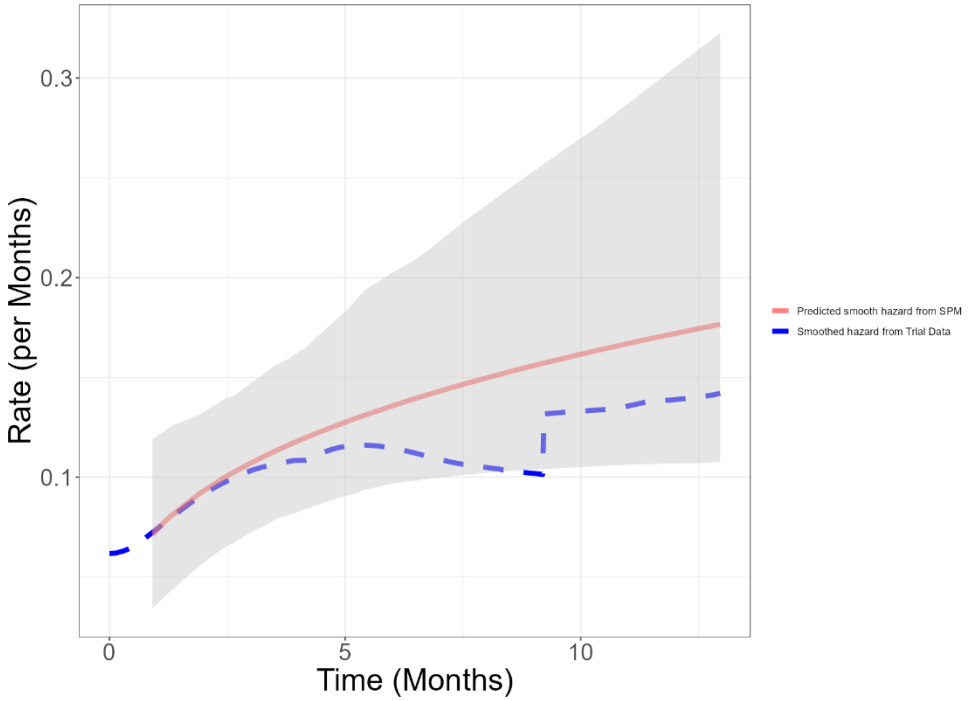
Chemotherapy - OS hazards

Figure 41: Comparison of the observed and predicted OS hazards for chemotherapy exponential SPM



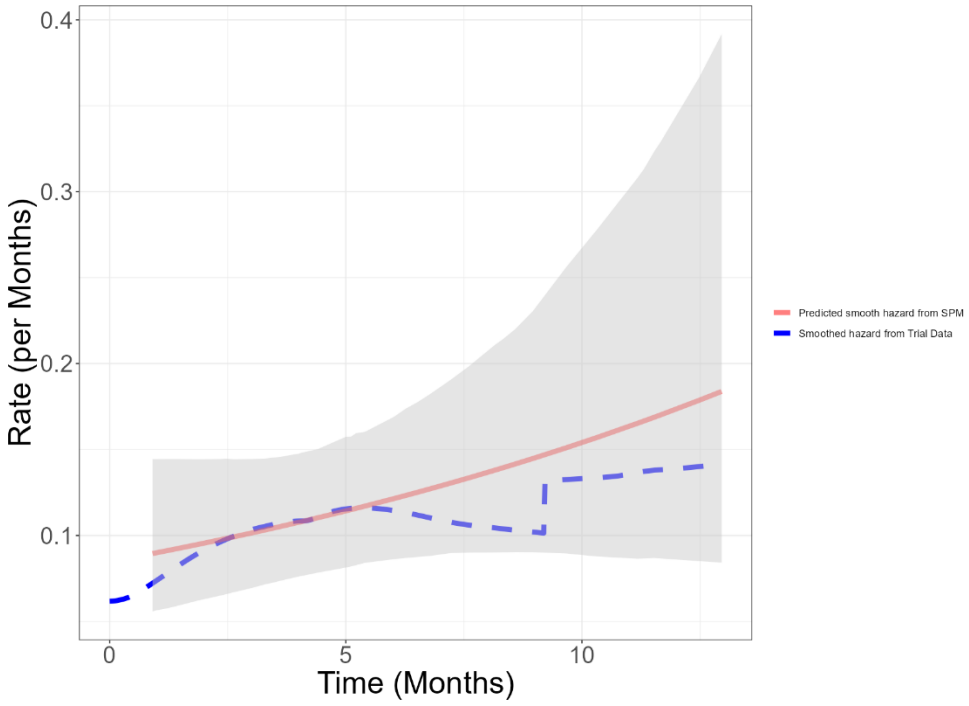
Abbreviations: OS, Overall survival; SPM, Standard parametric modelling.

Figure 42: Comparison of the observed and predicted OS hazards for chemotherapy Weibull SPM



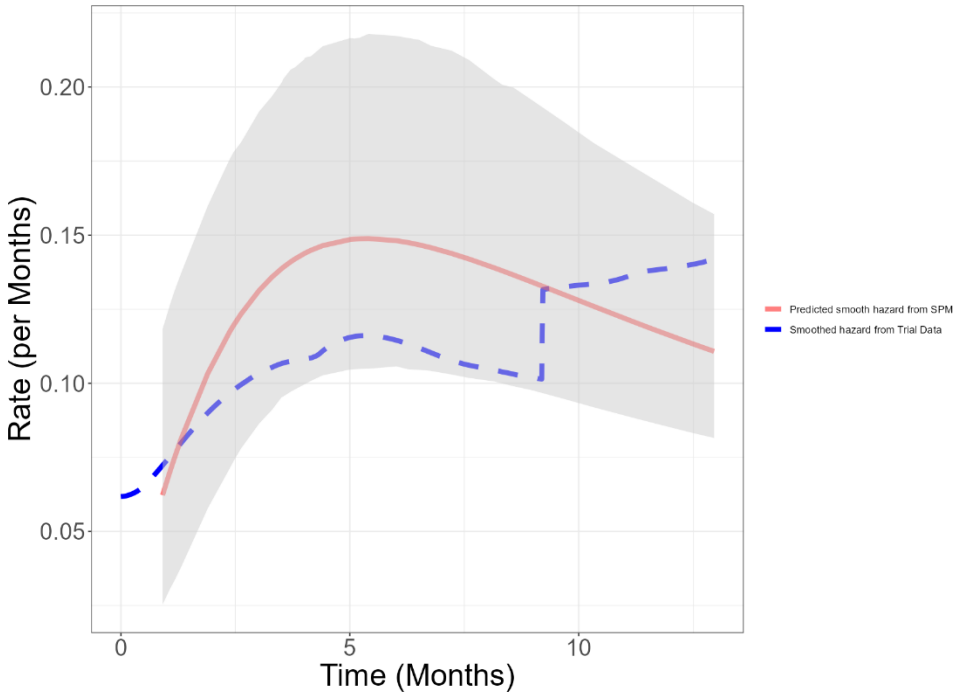
Abbreviations: OS, Overall survival; SPM, Standard parametric modelling.

Figure 43: Comparison of the observed and predicted OS hazards for chemotherapy Gompertz SPM



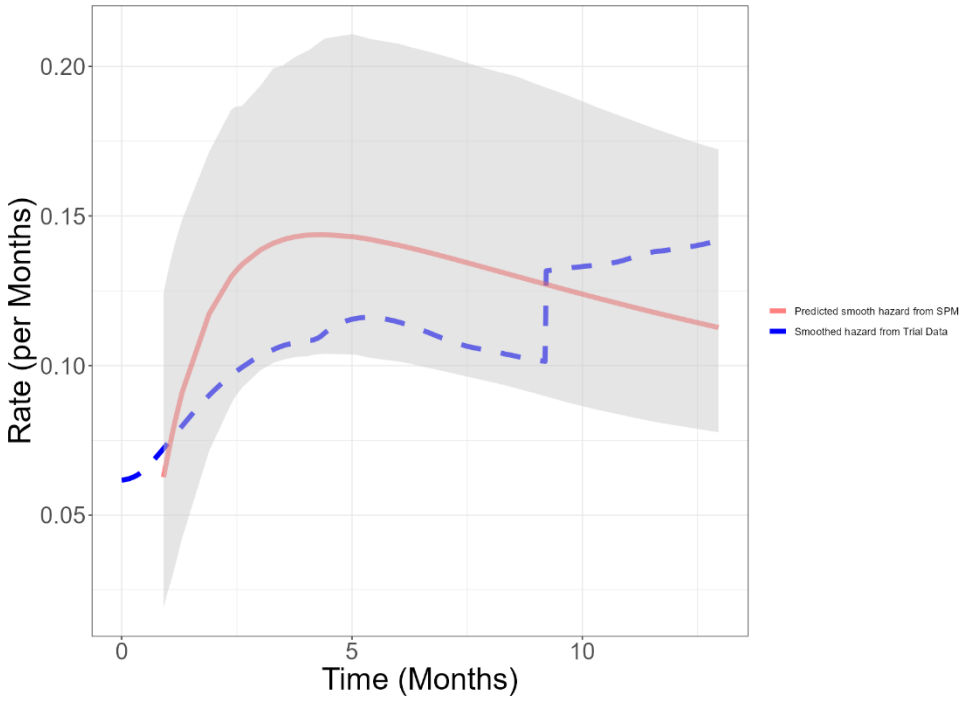
Abbreviations: OS, Overall survival; SPM, Standard parametric modelling.

Figure 44: Comparison of the observed and predicted OS hazards for chemotherapy log-logistic SPM



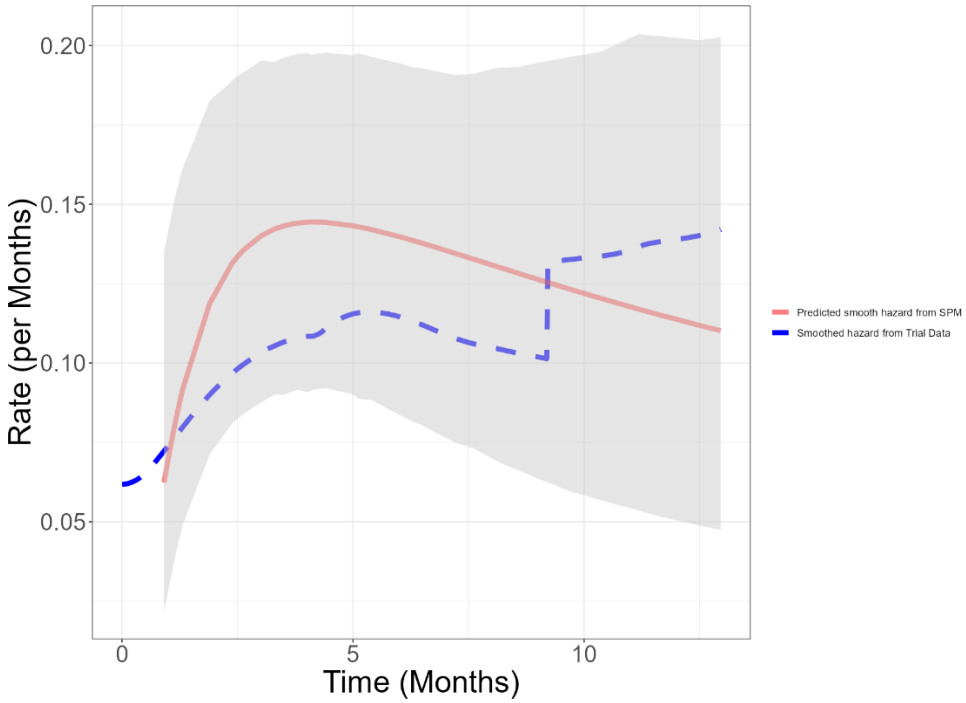
Abbreviations: OS, Overall survival; SPM, Standard parametric modelling.

Figure 45: Comparison of the observed and predicted OS hazards for chemotherapy log-normal SPM



Abbreviations: OS, Overall survival; SPM, Standard parametric modelling.

Figure 46: Comparison of the observed and predicted OS hazards for chemotherapy generalised gamma SPM



Abbreviations: OS, Overall survival; SPM, Standard parametric modelling.

B6. PRIORITY. CS, Section 3.3.1.5, Figure 22, page 142. None of the standard parametric survival models provide a good fit for ipilimumab monotherapy PFS. Please comment on this finding, and consider fitting more flexible models (e.g., spline models or MCMs) which may better reflect the turning points in the hazards.

Response: The Company is unable to perform spline-based modelling within the time frame provided for the clarification questions. In addition, an SPM approach was selected as more appropriate for decision-making than an MCM approach as detailed in the answer to B1. Given this, the Company have not presented a flexible model in response to this clarification question.

B7. PRIORITY. CS, Section, 3.3.1.1, page 125. The STC is incorporated into the economic model by applying the ratio of the STC-adjusted HR for lifileucel vs. ipilimumab divided by the STC-unadjusted HR for lifileucel vs. ipilimumab to the MCMs for the lifileucel group. The EAG considers this approach to be unconventional and difficult to interpret. Please clarify why this approach was taken and comment on the statistical interpretation of the HR-adjusted lifileucel arm.

Response: The Company acknowledges that the methodology used in this analysis is unconventional.

Regarding the KM curves, the unadjusted lifileucel curve has the longest follow-up period. However, the lifileucel curve adjusted for ipilimumab has a shorter follow-up and is influenced by the shape of the ipilimumab curve, thereby distorting the plateau observed in the data and curve extrapolation, as in the unadjusted curve. In contrast, the ipilimumab curve has a short follow-up period and a different shape with no plateau.

Given these limitations, the unadjusted lifileucel curve and its associated distributions were selected as the basis for any further adjustments aimed at obtaining accurate survival distributions for the lifileucel curve adjusted for ipilimumab.

Since a direct ratio between the adjusted and unadjusted lifileucel datasets was not available from the STC analysis, a proxy ratio based on the methodology described in our company submission (CS Section 3.3.1.1) was calculated and applied to estimate the distributions for the adjusted lifileucel dataset from those of the unadjusted dataset. The approach maintained the integrity of the curve shape from

the unadjusted to the adjusted curve.

B8. PRIORITY. CS, Section 3.3.1.5, Figure 27, page 152. None of the STC-adjusted MCMs provide a good visual fit to the STC-adjusted KM OS function. Please explain why this is the case.

Response: Due to the limited follow-up of ipilimumab trial (da Silva *et al.* 2021 [DOI: 10.1016/S1470-2045(21)00097-8]), the lifileucel OS KM curve adjusted for ipilimumab can only be projected up to approximately [redacted]. Additionally, after the adjustment for ipilimumab, the shape of lifileucel OS curve is impacted by the shape of the ipilimumab OS curve. As a result of the adjustment, the adjusted lifileucel curve does not exhibit a clear plateau. To account for this limitation, MCM was not applied to adjusted lifileucel OS curve. Instead, MCM was run on the unadjusted lifileucel KM curve and adjusted afterwards by using the ratio, as described in the CS section 3.3.1.1.

B9. CS, Section 3.3.1.5, Figure 21 (page 141) and Figure 27 (page 152). The footnotes to Figures 21 and 27 state that *"The difference between the follow up unadjusted lifileucel KM curve and adjusted lifileucel KM curve was due to how the company predicted when patients would still be at risk of an event (when there was at least one censored event)."* Please clarify how these adjusted KM functions were generated.

Response: The survival probability predictions were generated using the *predictSurvProb* function, and was applied up to the last time point there was an event for PFS and OS for lifileucel. The last event occurred in lifileucel arm at around [redacted], as such, the code estimates survival probability predictions for the adjusted lifileucel population up to this timepoint.

Treatment discontinuation

B10. PRIORITY. CS, Section 3.3.2, page 157. The executable model assumes that [redacted] of patients who undergo tumour resection for the production of lifileucel will receive the lifileucel infusion. This percentage is calculated based on the number of people in the PDAwCS analysis set (N=[redacted]) divided by [redacted]. Please clarify how the

denominator for this calculation was derived (i.e., specifically which patient/analysis set does the denominator relate to?).

Response: Overall, a total of 270 patients were screened within Cohorts 2 and 4. Of these, 189 patients had their tumour harvested (i.e. the tumour harvested [TH] set). The denominator for the discontinuation, [redacted] patients, is reflective of number of patients within the TH set with lifileucel manufactured at a commercially approved manufacturing site. Because no patient in the commercial setting would have lifileucel manufactured at a non-commercially available site, and because these patients are also removed from the discontinuation rate numerator, the Company only consider the [redacted] suitable to use as a denominator for the purposes of calculating the discontinuation.

Utility and disutility values

B11. CS, Sections 3.4.1 and 3.4.2, pages 159-161, Appendix K.3, pages 213-215, and Appendix N, pages 243-253. The CS mentions that the collection of HRQoL data in Study C-144-01 was not systematic and it was not considered robust compared to other studies to inform the model. Please clarify:

- Were EORTC QLQ-C30 data collected from patients after discontinuation (in those who did not receive the full lifileucel regimen) or after progression?

Response: Per trial protocol, EORTC QLQ-C30 data were collected until disease progression or start of new anticancer therapy. Also, again by trial protocol, EORTC QLQ-C30 data were not collected for patients who did not receive full lifileucel regimen.

- Why is the HRQoL analysis based on an earlier data cut-off (24th February 2022) compared with the clinical outcomes data cut (30th June 2023)?

Response: As the volume of EORTC QLQ-C30 assessments from 24th February 2022 cutoff (with 27.6 months of follow-up) were found sufficient and quality of life data was only an exploratory outcome of the study, later database-locks from the trial including 30th June 2023 cutoff were merely for updates to primary and secondary endpoints (e.g. ORR, PFS, OS and DoR).

- Appendix N, page 246. The text mentions that *"For each model, to handle missing data, patient visit dates with missing responses in required QLQ-C30 domains were excluded."*
    - Were imputation methods considered or used to handle missing data?

Response: Possibility of using data imputation methods were considered but they were not found appropriate. For each model considered for mapping QLQ-C30 data, if a patient's response was missing for one or more items required for that model's calculation, the corresponding visit was excluded from the mapped dataset for simplicity despite its impact on the sample size. This decision was based on (1) the exploratory nature of the QLQ-C30 data collection in the study, (2) the relatively small sample size available, and (3) the desire to minimize additional uncertainty and bias that would be introduced through imputation methods especially if missingness mechanism is not completely at random.

    - How many visits/assessments are related to each assessment time point in Appendix K.3, Table 59, page 215 (the text in Section 3.4.2 page 159 and Appendix N page 250 report a total of [redacted] visits/responses to the QLQ-C30 questionnaire)?

Response: Total number of assessments taken at each of the indicated landmark times should match with the indicated number of patients per trial protocol. For instance, for Cohorts 2 and 4 combined, at week 12, there were [redacted] patients and for each patient there was one assessment. Therefore, week measurements for this combined cohort are based on [redacted] assessments in total. In addition to the scheduled EORTC QLQ-C30 assessments, there were also unscheduled assessments throughout the follow-up. Therefore, for each cohort, total number of assessments across the follow-up can be more than the sum of the sample sizes across landmark time points.

In total, there were [redacted] mapped responses referring to all patient visits across the study where sufficient QLQ-C30 data were available to calculate an EQ-5D utility score using the crosswalk algorithms. These assessments were collected at variable time points depending on visit schedules (e.g., screening, pre-infusion, follow-up visits) and thus the assessments include a mix of baseline, early post-infusion, and later follow-up time points.

- Were any statistical models fitted to the mapped data?

Response: No new statistical models were fitted to the mapped utility data. EQ-5D utility values were derived by directly applying the published coefficients from the Kim *et al.* 2012 (10.1186/1477-7525-10-151) and Wojciechowski *et al.* 2023 (10.57264/cer-2022-0178) mapping models to the QLQ-C30 responses from the study. Descriptive statistics (means, medians, standard deviations, minimum, maximum) were calculated on the mapped utilities. However, no regression models, longitudinal models, or new predictive modelling were performed on the mapped data. This decision was consistent with minimizing additional transformation steps beyond the validated published mapping algorithms, and to maintain transparency in the use of mapped values.

- Please justify why the data from Study C-144-01 were not used to inform the model utility values - *the text in Section 3.4.2 page 160 suggests that the mean/median utility scores from the Kim and Wojciechowski models were in range/aligned with the values from the literature ("0.82 for patients in a progression free state, 0.69 for those in a progressed state, and between 0.8 and 0.95 for those achieving cure, depending on patient age"*).

Response: While the mapped utilities were consistent with published values for similar previously treated advanced melanoma populations, several limitations of the data led to the decision to not use these mapped values to inform model utilities directly in the cost-effectiveness analysis and to instead rely on published data as the primary input for modelling. These limitations were:

1. **Data Sparsity:** A significant proportion ([redacted]) of patients had only one or two QLQ-C30 assessments available and the average time between visits with assessments was [redacted] limiting the ability to reliably characterize changes in HRQoL over time or by health states (e.g., progression-free vs. progressed disease). Sparsity of the data in the trial was previously investigated and sources of inconsistencies contributing to data gaps were found in the administration of questionnaires (e.g. not always collecting surveys at baseline due to protocol misunderstandings, allowing patients to refuse participation in the questionnaire, not ensuring patients answered all questions when given the assessment).

2. **Exploratory Data Collection:** The quality-of-life data was only an exploratory outcome of the study, but its collection was not designed with the same rigor as primary endpoint or efficacy outcomes from the study. Therefore, collected data were not completely suitable to dress economic evaluation. When combined with the data sparsity, using utility scores mapped from the quality-of-life data collected in the trial would lead to high level of uncertainty in the results.
3. **Risk of Bias from Missing Data:** Missingness of quality of life data was not random in the study which could affect the statistical reliability of mapped utility estimates.
4. **Uncertainty in the Mapping:** Models used to map the QLQ-C30 scores to EQ-5D scores were based on different populations with differing demographics and disease characteristics (e.g. Korea, France). More importantly these candidate mapping models were not developed based on UK demographics. Therefore, utilization of such mapping models could have further confounding effects on the robustness of the mapped scores and their appropriateness as a direct input in economic modelling.

Overall, given that the mapped utility values were aligned relatively closely with existing EQ-5D scores reported from earlier appraisals in advanced melanoma, it was considered methodologically more robust to use published utility estimates directly rather than relying on sparsely populated, mapped trial-derived utilities.

B12. CS, Section 3.4.4, page 167. The model applies utility values for the PF and progressed disease (PD) health states which have been calculated as an unweighted average of utility values used in previous models used to inform several previous NICE technology appraisals (TAs), as well as two other published models reported in the literature. The EAG considers this approach to be unconventional and notes that some of the utility values included in the unweighted average do not relate to patients at the relevant lines of therapy for the lifileucel target population and some do not reflect EQ-5D-3L values. Please explain why this unweighted averaging approach was taken rather than selecting the most relevant and applicable source.

Response: The company acknowledges that some of the included utility values were not derived from the EQ-5D measure, such as those reported in Retel *et al.*

2018 study (DOI: https://doi.org/10.1186/s12885-018-4788-5), NICE TA269 (https://www.nice.org.uk/guidance/ta269) (which used the standard gamble method) and NICE TA319 (https://www.nice.org.uk/guidance/ta319) (which used the EORTC QLQ-C30). These studies were included to ensure that all relevant and available data were considered in the analysis.

To assess the impact of excluding these non-EQ-5D utility values, the company conducted additional analysis excluding utility values from Retel *et al.* 2018 (DOI: https://doi.org/10.1186/s12885-018-4788-5), NICE TA269 (https://www.nice.org.uk/guidance/ta269) and NICE TA319 (https://www.nice.org.uk/guidance/ta319). The removal of these values had the following effect on average utility values: the progression-free (PF) utility value decreased slightly from 0.77 to 0.76, while the progressed disease (PD) utility value increased from 0.67 to 0.70. The impact on the ICER was marginal, with a reduction of approximately [redacted], as shown in Table 7.

After excluding these non-EQ-5D utility values, the gap between PF and PD utility decreased. Therefore, the company considers the original approach of using all available data as more robust and aligned with the clinical expert's opinion (see question B13).

Table 7: Summary of health state utility values for cost-effectiveness analysis base-case and additional analysis

	Health state	Utility value: mean	Impact on the ICER
Base-case	PF (for all treatment arms)	0.77	--
	PD (for all treatment arms)	0.67	
Additional analysis	PF (for all treatment arms)	0.76	[redacted]
	PD (for all treatment arms)	0.70	

Abbreviations: PD, Progressed disease; PF, Progression-free, TA, Technology assessment, NICE, National Institute for Health and Care Excellence.

As stated in the Company Submission (CS), page 166, section 3.4.4, since lifileucel is considered a second-line treatment, PF utility values from NICE TAs and literature on first-line treatments were not considered. Instead, the company assumed that the PD utility values from first-line treatments are equivalent to the PF utility values for second-line treatment. This assumption is based on the rationale that patients who

progress from first-line treatment would experience a similar quality of life when receiving second-line treatment**.**

An unweighted average was used to combine utility values, consistent with the approach outlined in the NICE NG14 health economic model (https://www.nice.org.uk/guidance/ng14). This method was considered appropriate because all utility estimates were derived from relevant clinical trials included in the respective technology appraisals, and there was no clear rationale to assign greater weight to any particular estimate. Selecting a single most relevant source could introduce bias, especially in the absence of a clearly superior data set. By treating all eligible sources equally, the unweighted approach avoids privileging one study over another without strong justification.

B13. CS, Section 3.4.4, page 166. With reference to the utility values reported by Retel *et al.* (PF utility = 0.85, PD utility = 0.59), the CS states that *"...the panel expected a larger gap between PF and PD utility values, with a higher PF utility value."* However, the utility values applied in the company's model feature a comparatively smaller gap between the health states (PF utility = 0.77, PD utility = 0.67). Please comment on the face validity of the utility values applied in the economic model.

Response: During the ad-board meeting, the Retel *et al.* 2018 (DOI: https://doi.org/10.1186/s12885-018-4788-5) study was presented to the clinical experts. While no major concerns were raised, the KOLs generally agreed that the utility values were directionally consistent with their clinical experience. However, the KOLs expected a greater difference between the progression-free (PF) and post-disease progression (PD) health states, particularly anticipating a higher utility value for PF.

The company acknowledges this feedback but would like to highlight that the PF utility value was derived from a range of NICE TAs and published literature to minimise bias. The company considers its approach to be conservative, noting that the resulting PF utility value may be lower than what would be expected in clinical practice, potentially underestimating the quality-of-life (QoL) benefits associated with the PF state.

Although the observed gap between PF and PD utility values is smaller than

anticipated, it nonetheless reflects a meaningful difference in health-related quality of life (HRQoL) between the two health states. Additionally, a scenario with utility values from the Retel *et al.* 2018 (DOI: https://doi.org/10.1186/s12885-018-4788-5) study was conducted and presented in the company submission.

B14. CS, Section 3.4.6, page 168. With reference to the utility decrement related to lifileucel administration applied in the model, based on NICE TA975:

- Please clarify the relevance for the population in this current appraisal of the utility value for event-free survival of 0.91 from Kelly *et al.* 2015, given that this estimate was derived from adjusted Short Form-36 (SF-36) scores from the Swiss Childhood Cancer Survivor Study and was mapped to the Health Utilities Index Mark 2 (HUI-2).
- The lifileucel model includes a disutility value of 0.42 taken from Sung *et al.* which corresponds to the disutility of undergoing chemotherapy and was based on a Visual Analogue Scale (VAS) completed by 12 physicians who care for patients undergoing bone marrow transplantation. Why is this disutility value relevant for inclusion in the lifileucel model?
- Justify why the estimated disutility is applied only to patients requiring intensive care in ICU (20%).

Response: The utility value of 0.91 for event-free survival (EFS) was used in the NICE TA975 (https://www.nice.org.uk/guidance/ta9750) appraisal for tisagenlecleucel and is based on adjusted SF-36 scores from the Swiss Childhood Cancer Survivor Study, mapped to the Health Utilities Index Mark 2 (HUI-2). The company acknowledges that this value was not derived from EQ-5D data nor from an adult melanoma population. However, in the absence of directly applicable data for lifileucel, this value was used as part of a proxy to calculate the relative disutility associated with lifileucel administration, rather than as an absolute utility input. It provided a reference point for estimating the proportional utility decrement of lifileucel administration.

The disutility value of 0.42, sourced from Sung *et al.* 2003 (DOI: 10.1002/cncr.11098) was used in TA975 ((https://www.nice.org.uk/guidance/ta9750) to reflect the QoL impact of CAR-T cell therapy administration. While the methodology and population differ from those in lifileucel, this value was not applied directly to the lifileucel model

as lifileucel administration is considered to be less invasive than CAR-T treatment. Instead, it was used to inform a proportional utility decrement (46%) relative to the EFS utility of 0.91 in TA975. This ratio was then applied in the lifileucel model to estimate the temporary disutility associated with lifileucel administration in the progression-free (PF) state. The relative ratio provides a pragmatic approach in the absence of lifileucel-specific utility data.

Key opinion leaders (KOLs), during the advisory board, indicated that only a subset of patients receiving lifileucel, approximately 20%, are expected to require ICU admission, primarily in relation to IL-2 administration. Most patients are anticipated to experience mild, transient symptoms with limited impact on QoL. Therefore, applying the disutility proportionally to only 20% of the treated population more accurately reflects clinical experience and avoids overestimating the QoL impact of lifileucel administration. This approach incorporates disutility for the most severe cases while recognising the generally tolerable nature of lifileucel administration for the majority of patients.

Costs and resource use

B15. CS, Section 3.5.1.3, page 182. The CS states that the model assumes *"a mean dose of 3.6 in the base case as not all patients are expected to receive the full four maximum doses due to disease progression or toxicity concerns"*, based on data from the MDX-010 study (Hodi *et al.* 2010 [DOI:10.1056/NEJMoa1003466]). The model assumes that 100% of the acquisition and administration costs are applied in the first 3 treatment cycles and 60% is applied in the final cycle. However, because acquisition and administration costs are only applied to patients who remain progression-free in the model trace, the expected number of cycles of ipilimumab received is already lower than 4 full cycles. Does the adopted approach underestimate the expected costs of ipilimumab?

Response: The company acknowledges that the adopted approach underestimates the expected costs of ipilimumab. An adjustment has been made to the model so that the acquisition and administration costs for a mean dose of 3.6 for ipilimumab are considered in the first cycle of the model, where all patients are progression-free. This change resulted in a decrease of the ICER between lifileucel and ipilimumab by

approximately [redacted] per QALY. Results of the cost-effectiveness analysis with all model changes implemented are presented in Table 9 to Table 12.

B16. PRIORITY. Company's advisory board meeting minutes (CS reference #16), page 10. The clinical experts who attended this meeting mentioned that the adoption of lifileucel would require logistics support, training and operational support. However, these costs are not included in the economic model. Please include these costs in the model or justify their exclusion.

Response: The Company expects hospitals that adopt lifileucel in the UK to all have existing cell therapy capabilities. While cell therapy naïve hospitals may require substantial training, process development, and a staff member providing operational and logistics support (i.e. a cell therapy coordinator), hospitals already offering cell therapy should have staffing and internal processes in place. Lifileucel at the expected volume for centres should not require additional staffing. Iovance provides a robust onboarding process and substantial ongoing operational support for no extra charge, including onsite and virtual support from the ATC Operations, virtual support from Case Manager teams, proactive and just-in-time tumour education from our Peer-to-Peer team. On demand on-site or virtual support is always available. Iovance provides a fully developed training program and SOPs that are ready for immediate treatment centre adoption/utilization. Training on the Iovance processes and the Chain-of-Identity/Chain-of-Custody system is delivered at onboarding, as needed based on centre needs, and with SOP changes. Therefore, the Company believes these costs are not warranted to be included.

B17. CS, Section 3.5.2, Table 77 (page 187) and model 'Data Store' worksheet, cells D262:D263, M270:M273 and H270:K273. In relation to the health state costs used in the model:

- The unit costs relative to 'Oncology/general ward - inpatient' and 'Palliative care unit – inpatient' (cells M270:M273) correspond to the 'excess bed days' and 'average cost per bed day'. Please clarify if the frequencies per cycle for these resources in cells H270:K273 correspond to the number of days or episodes per patient.
- The unit cost for 'Palliative care physician visit- outpatient' (cells D262:D263) corresponds to an unweighted average of outpatient medical and non-medical

specialist palliative care attendance (19 years and over) from PSSRU 2023. Please justify the use of non-medical specialist palliative care attendance in this unit cost.

Response: The resource use for 'Oncology/general ward – inpatient' was taken from NICE TA400 (Nivolumab in combination with ipilimumab for treating advanced melanoma [https://www.nice.org.uk/guidance/ta400]). The unit costs associated with this resource use reflects those adopted in the Company's submission and therefore the resource use is assumed to represent 'excess bed days'. Similarly, the resource use for 'Palliative care unit – inpatient' was also sourced form NICE TA400 (https://www.nice.org.uk/guidance/ta400). The unit cost used referenced in NICE TA400 (https://www.nice.org.uk/guidance/ta400) was based on the NHS National Schedule of Reference costs 2014/2015 (Average of total for SD01A and SD03A). As these specific codes are no longer available in the latest NHS reference costs, an equivalent unit cost was sourced from the PSSRU 2023 (https://kar.kent.ac.uk/id/eprint/105685). Given that all unit costs reflect a daily rate of hospital stay, the corresponding frequencies per cycle are interpreted as the number of days per patient.

The company included both outpatient medical and non-medical specialist palliative care attendance to ensure the costs appropriately reflected the potential costs associated with 'Palliative care physician visit- outpatient'. PSSRU 2023 did not provide weightings, so an unweighted average was utilised instead. The company updated the cost to be medical specialists only, thereby slightly increasing the unit cost, which had minimal impact on the ICER.

B18. CS, Section 3.5.2.1, page 190. Please provide details of which values for health care and social care cost estimates from Round *et al.* (2015) were used to obtain the estimate of £6,361.77 (uninflated value) used for the end-of-life costs in the model.

Response: The company acknowledges that the description in the submission was not specific enough. The value of £6,361.77 was taken from NICE TA627 (https://www.nice.org.uk/guidance/ta627), which reflected 2017/18 costs and inflated it to get £7,428.05. This value is very similar to the value used in TA950

(https://www.nice.org.uk/guidance/ta950) (£7,679.48). Impact of different values for end-of-life costs on the ICER is minimal.

Adverse events

B19. CS, Section 3.3.3, Table 54, page 158. The model includes lifileucel-related AEs only for those patients who receive the infusion, based on the Safety Analysis Set ('All patients who received any lifileucel infusion'). This approach implies that patients who undergo the tumour harvest but who do not receive the within-specification infusion do not experience any additional non-fatal lifileucel regimen-related AEs, except for those AEs applied to BSC/ipilimumab/chemotherapy after failure of the infusion. Please include these additional AEs in the model for patients in whom lifileucel is planned but not infused.

Response: The company acknowledges that patients who undergo the tumour harvest but who do not receive the within-specification dose, but do receive the out of specification dose, may still experience non-fatal lifileucel regimen-related AEs. The company has therefore included these additional AEs costs in the model ("Trace (Lifileucel)" – cell EC22) for these patients. It had minimal impact on the ICER. Results of the cost-effectiveness analysis with all model changes implemented are presented in Table 9 to Table 12.

B20. CS, Section 3.5.3, page 193 and Table 81. The CS states in relation to the cost of diarrhoea or colitis that *"around 30% of patients receiving infliximab would require an endoscopy, and the majority of these patients would subsequently need treatment with vedolizumab."* The EAG is unsure who "these patients" refers to. Please clarify what the company intended to assume regarding the percentage of patients who would require further treatment with vedolizumab. In addition, the information in Table 81 reports that 30% of patients receiving infliximab would receive vedolizumab whilst 80% of patients receiving infliximab would undergo endoscopy. Please confirm which proportions are correct.

Response: The company confirms a labelling error in Table 81, where the headings for endoscopy and vedolizumab were inadvertently switched. However, we confirm that the model calculations were performed correctly, based on the intended clinical assumptions. The company also recognised that the phrasing "*the majority of these*

patients would subsequently need treatment with vedolizumab" may have led to confusion. To clarify, based on clinical validation with UK key opinion leaders KOLs, it was established that some patients receiving infliximab would require endoscopy (30%), while the majority of patients receiving infliximab would receive vedolizumab (80%).

Uncertainty analysis

B21. CS, Section 3.4.4., Table 57, page 167. The 95% confidence intervals (CIs) for the utility values for the PF and PD health states overlap and these parameters are independently sampled in the executable model. This means that the sampled utility value for the PD state is frequently higher than the sampled utility value for the PF state in the same probabilistic model run. Ren *et al.* (*Pharmacoeconomics*, 2018, vol. 36[3]) have proposed a method for sampling ordered parameters, including utility values. Please apply this method in the model.

Response: While the method proposed by Ren *et al.* 2018 (DOI: 10.1007/s40273-017-0584-3) offer a formal approach for sampling ordered parameters, this method requires a significant amount of time and is not feasible to implement it at this stage.

As a practical and transparent alternative, the company has applied a cap that ensures the utility associated with PD does not exceed that of the PF health state when running probabilistic sensitivity analyses. Results of the cost-effectiveness analysis with all model changes implemented are presented in Table 9 to Table 12.

Additionally, during the call with NICE and EAG (16th April), EAG noted that there is a difference between deterministic and probabilistic ICER and asked for a justification. The probabilistic sensitivity analysis incorporates uncertainty around key parameter estimates by assigning probability distributions to them. However, if non-symmetric distributions (like for example Beta or Gamma) are chosen for uncertain parameters, this can lead to a range of potential outcomes, resulting in a spread of ICER values that may not match the single deterministic value.

Discount rates

B22. CS, Section 3.2.2.5, Table 29, pages 108-109. The CS argues that NICE's criteria for non-reference case discount rates are met for lifileucel. The economic

model indicates that approximately [redacted] of patients in the lifileucel group will receive the infusion and cure will be achieved in up to around [redacted] of these patients. Given that cure is not expected for more than [redacted] of patients in whom lifileucel infusion is planned, please provide further justification regarding why the company believes that the criteria for non-reference case discounting are met for lifileucel.

Response: The manufacturer agrees with the EAG that the NICE criteria for the non-reference discount rate is most applicable to the cured group, as this group most clearly is likely to have full or near-full health restored while meeting the other two criteria: (1) would otherwise die or have a very severely impaired life and (2) is likely to see benefits sustained over a very long period. With this in mind, in economic evaluations, starting from the time of cure, which is assumed to be year 3 in the base case analysis, an effective discount rate considering the corresponding fractions of cured and uncured patients in the surviving population with 1.5% and 3.5% discount rates on an annual basis, respectively, could be used to account for the possibility of cure. As the resulting effective discount rate is expected to be less than 3.5%, presented results in evidence submission obtained under the 3.5% annual discount rate can be interpreted as conservative.

Model implementation

B23. Executable model, worksheet “Survival Analysis – PFS”, columns DI:DN. Please clarify what these calculations are intended to do. A worked example may be useful.

Response: The formula estimates survival of the uncured fraction out of total population receiving lifileucel.
Please find below explanation of the formula, with cell DI15 as an example:

- The exact formula in the model is: DI15 = CU15-(CU15*DA15),
- This can be written in a format of: DI15 = (1-DA15)*CU15,
- DA15 is a PFS cure rate adjusted by the general population survival, and reflects the proportion of patients who are PFS-cured over time,
- (1-DA15) is a proportion of patients who are PFS-uncured,
- CU15 is a PFS of uncured population over time.

The formula multiplies the proportion of PFS-uncured population by its progression free survival.

B24. Executable model, worksheet “Data Store” cells D408:E509. The model uses life tables for the UK (2020-2022). Please amend the model to use life tables for England based on the most recent release.

Response: The company has amended the life tables to use the UK (2021-2023) as of the most recent release (18th March 2025). The impact on the ICER was minimal. Results of the cost-effectiveness analysis with all model changes implemented are presented in Table 9 to Table 12.

B25. Executable model, worksheet “Data Store”, cells C407:M510. These calculations are intended to estimate general population mortality rates per weekly model cycle, taking into account the proportion of males and females who are alive by age. However, the age distribution from Study C-144-01 applied in columns G:J is applied from age 0 years, rather than from age [redacted] years. Please confirm that this is an error and amend it in a corrected version of the model.

Response: The proportion of males and females was derived from the C-144-01 trial and assumed to be independent of age. Therefore, the proportion has been applied to all age groups. This enables changing of the baseline age for scenario analyses and allows for variation through the probabilistic sensitivity analysis.

B26. Executable model, worksheet “Data Store”, cells M407:M510. The formulae assume that there are 52 weeks per year. However, there 52.18 weeks per year (i.e., 365.25/7). Please confirm that this is an error and amend it in a corrected version of the model.

Response: The company acknowledges that this was an error and has been corrected. The impact on the ICER was minimal. Results of the cost-effectiveness analysis with all model changes implemented are presented in Table 9 to Table 12.

B27. Executable model, all model trace worksheets. All calculations of life years gained and QALYs gained are adjusted for the cycle length based on “(cycles/time)”. The variable “cycles” has a value of [redacted] and the variable “time” has a value of [redacted]. However, [redacted] is not equal to the number of weeks per year (i.e., the formula above gives 52.1875 rather than 52.1785). Please correct this throughout the model and ensure that the intended number of model cycles are still included in the time horizon of the corrected model.

Response: The company acknowledges that this was an error and has been corrected. The impact on the ICER was minimal. Results of the cost-effectiveness analysis with all model changes implemented are presented in Table 9 to Table 12.

B28. Executable model, all model trace worksheets, column C. The model includes 54 weekly cycles in year "0" and 52 weekly cycles in all other years within the time horizon. Please confirm that this is an error and amend it in a corrected version of the model.

Response: The company acknowledges that this was an error and has been corrected. The impact on the ICER was minimal. Results of the cost-effectiveness analysis with all model changes implemented are presented in Table 9 to Table 12.

B29. Executable model, worksheet "Data Store", cells S409:S510. These formulae return an age-adjusted multiplier for general population EQ-5D-3L at each given age relative to a starting age of [redacted] years. However, when the function "Age_adj_setting_fs" is set equal to "No", this cell range returns the EQ-5D-3L estimate for the general population at age [redacted], rather than a multiplier of 1.0. Please confirm that this is an error and amend it in a corrected version of the model.

Response: The company acknowledges that this was an error and has been corrected.

B30. Executable model, worksheet "Trace (Ipilimumab)", column AN. The formulae include a function "IF($C9<Ipi_cure_timepoint,Ipi_PFS_utility,1)" which assumes that patients experience perfect health after the cure time point (3 years). The EAG believes that this function should instead return the general population EQ-5D-3L value at age [redacted] (because age-adjustment of utility is already captured in the latter part of the overall function. Please note that the same issue applies in the worksheet "Trace (Lifileucel)", column DF. Please confirm that this is an error and amend it in a corrected version of the model.

Response: The company acknowledges that this was an error and has been corrected. As a result of this change the ICER increased by approximately [redacted] per QALY between lifileucel and ipilimumab. Results of the cost-effectiveness analysis with all model changes implemented are presented in Table 9 to Table 12.

B31. Executable model, worksheet "Data Store", cells O234:O241. The model

assumes that all chemotherapy regimens are given for a fixed duration of 1.49 months (approximately 45.3 days). Dacarbazine treatment is given on day 1 and then once every 21 days. The model cost calculations assume that 2.16 x 21-day cycles of dacarbazine can be given in 1.49 months. However, dacarbazine treatment is given on Day 1 of each cycle with the next 20 days off-treatment. Therefore, within the first 1.49 months, patients would have 3 treatment days (Day 1, Day 22 and Day 44) rather than 2.16 treatment days. This affects the acquisition and administration costs for all chemotherapy regimens included in the model. Please confirm that this is an error and correct this in a revised version of the model.

Response: The company acknowledges that this was an error and has been corrected. Results of the cost-effectiveness analysis with all model changes implemented are presented in Table 9 to Table 12.

B32. Executable model, worksheet “Data Store”, cell O235. The model applies an administration cost of £283.17 for temozolomide on every day that the patient takes a pill. This means that the administration cost is applied 8.1 times in 1.49 months. This appears to substantially overestimate the costs of temozolomide administration. Please confirm that this is an error and correct this in a revised version of the model.

Response: The company acknowledges that this was an error and has been corrected. The cost of oral administration has been applied as a one-off cost for temozolomide administration. The impact on the ICER was minimal. Results of the cost-effectiveness analysis with all model changes implemented are presented in Table 9 to Table 12.

B33. PRIORITY. Executable model, worksheet “Data Store” Cell L127:L128. The formula used to calculate the weighted costs for the biopsy on musculoskeletal site (as part of the costs of tumour procurement for patients receiving lifileucel) refers to the wrong column for the number of cases (column I instead of column H). Please confirm that this is an error and amend it in a corrected version of the model.

Response: The company acknowledges that this was an error and has been corrected. The cost of the biopsy dropped from £1,907.78 to £1,386.18. The impact on the ICER was minimal. Results of the cost-effectiveness analysis with all model changes implemented are presented in Table 9 to Table 12.

Section C: Textual clarification and additional points

C1. CS, Section 3.5.2., Table 77, pages 187-189 and model worksheet 'Data Store' cells F256:F299 and M256:Q299. Most of the unit costs shown in Table 77 do not match the values used in the model. In addition, some of the codes used in NHS reference costs do not match between the table and model (e.g., complete blood count is referred to as 'TOC currency code DAPS05' in the CS, and 'Other currency code PATH04' in the model). Please clarify which values and codes are correct and update the model if necessary.

Response: The company acknowledges a discrepancy between CS table 77 and the model worksheet. As the model worksheet contains the most up-to-date data, no changes to the model were made (except of one change in response to B17). Please find below the revised and most current version of unit costs and resource use per patient (Table 8).

Table 8: Unit costs and resource use per patient

Resource	Unit cost inflated to 2023/24 (£)	Health state	Resource use per cycle (per week)				Source (unit cost)
			Lifileucel	BSC	Chemotherapy	Ipilimumab	
Medical oncologist visit – outpatient	193.39	PF	0.35	0.35	0.35	0.35	NHS reference costs 2023/24 (https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/) Medical Oncology (Total OPATT service code 370).
		PD	0.13	0.13	0.13	0.13	
Radiation oncologist visit- outpatient	159.94	PF	0.01	0.01	0.01	0.01	NHS reference costs 2023/24 (https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/) Clinical Oncology Previously Radiotherapy (Total OPATT service code 800).
		PD	0.02	0.02	0.02	0.02	
GP visit - outpatient	38.00	PF	0.02	0.02	0.02	0.02	PSSRU 2023 (https://kar.kent.ac.uk/id/eprint/105685): pg64 without qualifications excluding direct costs.
		PD	0.34	0.34	0.34	0.34	
Palliative care physician visit- outpatient	243.00	PF	0.00	0.00	0.00	0.00	PSSRU 2023 (https://kar.kent.ac.uk/id/eprint/105685): pg36 outpatient medical specialist palliative care attendance (19 years and over)
		PD	0.06	0.06	0.06	0.06	
Psychologist visit- outpatient	167.20	PF	0.00	0.00	0.00	0.00	PSSRU 2014: pg183 per hour of client contact. 1 hour visit assumed. (From NICE TA400 - https://www.nice.org.uk/guidance/ta400)
		PD	0.02	0.02	0.02	0.02	
Plastic surgeon visit- outpatient	160.87	PF	0.01	0.01	0.01	0.01	NHS reference costs 2023/24 (https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/) Plastic Surgery (Total OPATT service code 160)
		PD	0.00	0.00	0.00	0.00	
Nurse visit- outpatient	58.11	PF	0.03	0.03	0.03	0.03	NHS reference costs 2023/24 (https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/) District Nurse, Adult, Face to face (TOC currency code N02AF)
		PD	0.00	0.00	0.00	0.00	
Oncology/general ward – inpatient	367.08	PF	0.01	0.01	0.01	0.01	NHS reference costs 2023/24 (https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/) Weighted average of excess bed days for elective and non-elective inpatients for all HRGs
		PD	0.11	0.11	0.11	0.11	

Palliative care unit – inpatient	305.00	PF	0.00	0.00	0.00	0.00	PSSRU 2023 (https://kar.kent.ac.uk/id/eprint/105685): pg 36 Inpatient, specialist palliative care (19 years and over), average cost per bed day (19 years and over)
		PD	0.23	0.23	0.23	0.23	
Palliative care physician - home care	92.00	PF	0.00	0.00	0.00	0.00	PSSRU 2023 (https://kar.kent.ac.uk/id/eprint/105685): pg36 Outpatient - non medical specialist palliative care attendance.
		PD	0.05	0.05	0.05	0.05	
Palliative care nurse - home care	142.34	PF	0.00	0.00	0.00	0.00	NHS reference costs 2023/24 (https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/) Specialist Nursing, Palliative/Respite Care, Adult, Face to face (TOC currency code N21AF)
		PD	0.20	0.20	0.20	0.20	
Home aide visits	243.00	PF	0.00	0.00	0.00	0.00	PSSRU 2023 (https://kar.kent.ac.uk/id/eprint/105685): pg36 Outpatient - medical specialist palliative care attendance (19 years and over).
		PD	0.43	0.43	0.43	0.43	
CT scan	113.71	PF	0.23	0.23	0.23	0.23	NHS reference costs 2023/24 (https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/) Average of total for RD20A/RD21A/RD22Z.
		PD	0.01	0.01	0.01	0.01	
MRI of brain	171.92	PF	0.01	0.01	0.01	0.01	NHS reference costs 2023/24 (https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/) Average of total for RD01A/RD02A/RD03Z.
		PD	0.00	0.00	0.00	0.00	
Chest X-ray	168.16	PF	0.07	0.07	0.07	0.07	NHS reference costs 2023/24 (https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/) Contrast Fluoroscopy Procedures with duration of less than 20 minutes RD30Z (Total HRG).
		PD	0.00	0.00	0.00	0.00	
PET scan	613.44	PF	0.00	0.00	0.00	0.00	NHS reference costs 2023/24 (https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/) Positron Emission Tomography, 19 years and over RN07A (Total HRG).
		PD	0.00	0.00	0.00	0.00	
Bone scintigraphy	498.45	PF	0.00	0.00	0.00	0.00	NHS reference costs 2023/24 (https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/) Nuclear Bone Scan of two or three phases, 19 years and over RN15A (Total HRG).
		PD	0.00	0.00	0.00	0.00	
Echography	123.07	PF	0.01	0.01	0.01	0.01	

		PD	0.00	0.00	0.00	0.00	NHS reference costs 2023/24 (https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/) Weighted average of total for RD23Z/RD24Z/RD25Z/RD26Z/RD27Z.
Complete blood count	3.10	PF	0.30	0.30	0.30	0.30	NHS reference costs 2023/24 (https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/) Haematology (Other currency code PATH05)
		PD	0.00	0.00	0.00	0.00	
Complete metabolic panel	1.53	PF	0.28	0.28	0.28	0.28	NHS reference costs 2023/24 (https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/) Haematology (Other currency code PATH04)
		PD	0.00	0.00	0.00	0.00	
Lactate dehydrogenase	1.53	PF	0.28	0.28	0.28	0.28	NHS reference costs 2023/24 (https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/) Haematology (Other currency code PATH04)
		PD	0.00	0.00	0.00	0.00	
Pain management	211.48	PF	0.00	0.00	0.00	0.00	Total pain control management unit costs. (From NICE TA400 - https://www.nice.org.uk/guidance/ta400)
		PD	0.39	0.39	0.39	0.39	
Total cost (£)		**PF**	**121.16**	**121.16**	**121.16**	**121.16**	
		PD	**391.85**	**391.85**	**391.85**	**391.85**	

C2. CS, Section 3.5.3, page 194. The estimated total cost of managing Grade 3+ diarrhoea/colitis reported in the CS does not match the value used in the model (£5,164.79 versus £5,162.07). Please clarify why there is a discrepancy and confirm which value is correct. Amend the model if necessary.

Response: The company acknowledges that this was an error in the CS (page 193) and the correct value is £5,162.07, as per the model.

C3. CS, Section 3.4.4, page 167. The EAG was unable to verify the values reported for the utility values from NICE TA319 (Placebo +DTIC= 0.84 and Ipilimumab + DTIC 0.83) in the correspondent reference. Please clarify where these values are reported in the in TA319 documents or explain how these values were estimated from values reported in TA319.

Response: The utility values from NICE TA319 were taken from Table 41 in the TA319 STA company submission (https://www.nice.org.uk/guidance/ta319). The exact values taken from this table were 0.8383 (SD 0.1433) for placebo + DTIC and 0.8298 (SD 0.1357) for Ipilimumab + DTIC, which were rounded to two significant figures. This resulted in the final figures used in the model of 0.84 and 0.83 respectively.

Section D: Updated base case results of the cost-effectiveness analysis

Table 9: Deterministic base case results of lifileucel with the PAS price versus ipilimumab using a 1.7 disease severity modifier

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (including 1.7 disease severity modifier)	ICER incremental (£/QALY)
Lifileucel	[redacted]	[redacted]	4.07	-	-	-	-
Ipilimumab	[redacted]	[redacted]	0.87	[redacted]	[redacted]	5.44	[redacted]

Abbreviations: BSC, Best supportive care; ICER, Incremental cost-effectiveness ratio; LYG, Life years gained; PAS, Patient access scheme; QALYs, Quality-adjusted life years.
Note: 1.7 disease severity modifier has been applied to the incremental QALYs.

Table 10: Deterministic base case results of lifileucel with the PAS price versus BSC and chemotherapy using a 1.7 disease severity modifier

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (including 1.7 disease severity modifier)	ICER incremental (£/QALY)
Lifileucel	[redacted]	[redacted]	2.87	-	-	-	-
BSC	[redacted]	[redacted]	0.29	[redacted]	[redacted]	4.38	[redacted]
Chemotherapy	[redacted]	[redacted]	0.56	[redacted]	[redacted]	3.92	[redacted]

Abbreviations: BSC, Best supportive care; ICER, Incremental cost-effectiveness ratio; LYG, Life years gained; PAS, Patient access scheme; QALY, Quality-adjusted life years.
Note: 1.7 disease severity modifier has been applied to the incremental QALYs.

Table 11: PSA base case results of lifileucel with the PAS price versus ipilimumab using a 1.7 disease severity modifier

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs (including 1.7 disease severity modifier)	ICER incremental (£/QALY)
Lifileucel	[redacted]	4.136	-	-	-
Ipilimumab	[redacted]	0.834	[redacted]	5.613	[redacted]

Abbreviations: BSC, Best supportive care; ICER, Incremental cost-effectiveness ratio; LYG, Life years gained; PAS, Patient access scheme; QALYs, Quality-adjusted life years.
Note: 1.7 disease severity modifier has been applied to the incremental QALYs.

Table 12: PSA base case results of lifileucel with the PAS price versus BSC and chemotherapy using a 1.7 disease severity modifier

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs (including 1.7 disease severity modifier)	ICER incremental (£/QALY)
Lifileucel	[redacted]	2.983	-	-	-
BSC	[redacted]	0.290	[redacted]	4.578	[redacted]
Chemotherapy	[redacted]	0.557	[redacted]	4.123	[redacted]

Abbreviations: BSC, Best supportive care; ICER, Incremental cost-effectiveness ratio; LYG, Life years gained; PAS, Patient access scheme; QALY, Quality-adjusted life years.
Note: 1.7 disease severity modifier has been applied to the incremental QALYs.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Lifileucel for previously treated unresectable or metastatic melanoma [ID3863]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **3 October 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating unresectable or metastatic melanoma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	James Larkin
2. Name of organisation	Royal Marsden NHS Foundation Trust
3. Job title or position	Consultant Medical Oncologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with unresectable or metastatic melanoma? ☒ A specialist in the clinical evidence base for unresectable or metastatic melanoma or technology. ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NA
8. What is the main aim of treatment for unresectable or metastatic melanoma?	Cure

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Durable response to treatment; a response duration of over a year is significant
10. In your view, is there an unmet need for patients and healthcare professionals in unresectable or metastatic melanoma?	Yes
11. How is unresectable or metastatic melanoma currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Checkpoint inhibitor therapy, principally nivolumab + ipilimumab or + relatlimab is current standard of care Pathway of care is well defined Checkpoint inhibitor therapy is only effective for ~50% of those with metastatic melanoma. Currently there are no effective reimbursed therapies in the refractory setting and lifileucel has show durable benefit in about a third of patients in this setting.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Lifileucel is a one-off polyclonal TIL therapy so very different from currently used drug treatments for advanced melanoma It should be used in experienced specialised centres with both melanoma and cellular therapy expertise

13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes as above See 5 year data from lifileucel registration cohort (Medina at el ASCO 2025)
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Yes as above
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Inclusion criteria as per registrational cohort
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen	No

may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes; first ever approved cellular therapy for a solid tumour
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Yes related to administration of therapy see e.g. Chesney et al JITC 2022
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA268]?	No

23. How do data on real-world experience compare with the trial data?	No RWE reported yet
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	NA

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Lifileucel for previously treated unresectable or metastatic melanoma [ID3863]

Clinical expert statement

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Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating unresectable or metastatic melanoma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Heather Shaw
2. Name of organisation	University College London Hospital NHS Foundation Trust (for Melanoma Focus)
3. Job title or position	Consultant Medical Oncologist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with unresectable or metastatic melanoma? ☐ A specialist in the clinical evidence base for unresectable or metastatic melanoma or technology. ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for unresectable or metastatic melanoma?	Ideally to cure the condition or at least produce long term control (many months/years) with good quality of life

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Reduction in volume or resolution (consistent with recognised descriptions of partial and complete response) of radiologic melanoma lesions which is maintained over time (see Q8)
10. In your view, is there an unmet need for patients and healthcare professionals in unresectable or metastatic melanoma?	Yes – if patients progress beyond current approved therapies, particularly progression on or after immunotherapy means there are no further long term or curative options available – data for the cellular therapy category suggests that this would no longer be the case if TIL were accessible to patients with advanced melanoma. There are a proportion (approx 30%) who will respond to TIL therapy when they have not responded to or progressed after exposure to currently approved treatments – a subset of these patients will have long term control and there appears to be little in the way of significant long term side effect profile.
11. How is unresectable or metastatic melanoma currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Advanced melanoma is currently treated to NICE guideline NG14 which is supported by significant clinical trial data embedded in its recommendations and fits with the pathway followed throughout England/Wales/NI. While there may be some minor variation between cancer centres and clinicians – the principles and approach are widely accepted without major outlying opinion. The part of the pathway that this technology would currently influence would generally be section 1.8.12 and 14 which reference DTIC chemotherapy or best supportive care – chemotherapy has low rates of response in advanced melanoma and does not sustain long term control even in those who respond. For patients who are fit enough and deemed suitable – TIL therapy would be potentially a far more meaningful and possibly life saving intervention compared to the current standard in the same step of the therapy pathway.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The equivalent current standard of care at the point of TIL delivery in the melanoma pathways would be in place of clinical trial/chemotherapy or best supportive care depending on the patient and their suitability.

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	This would require more resource due to the complexity and intensity of the TIL delivery process and could only be managed in centres who are conversant with JACIE, have access to appropriate surgical procurement under HTA licence and then experience with high dose chemotherapy, cellular product handling and delivery, and IL2 management including access to higher care facilities such as HDU/ITU if needed. This will need selection of these centres for TIL delivery in the first instance and then perhaps further waves with relevant training etc for other centres if demand is such that this is judged necessary. These centres may require support/mentoring from established centres and input with accreditation and licencing etc.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	The technology will undoubtedly provide a tranche of patients with improvements over currently available care at the point of the pathway that it is being recommended for – it would both increase length of life and quality for those who respond given the alternative would be ineffective chemotherapy or best supportive care for the majority. Data from NIH (which uses a version of the process described for the product being reviewed) shows that patients can benefit for years from a single cell infusion (and the process around it).
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There are those who are intolerant of checkpoint inhibitors and require to stop due to severe (but reversible) side effects who cannot be safely rechallenged and who have not responded to therapy – they would have the potential to benefit from TIL type of therapy (assuming fit enough to do so) in addition to those who have “traditionally” progressed through treatment. Those who are not fit enough for subsequent lines of therapy would not be considered for TIL type treatment as it would not be tolerable and would be a major undertaking that is unlikely to provide benefit.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use?	It is complex and intense therapy versus the equivalent current care but the potential for significant gain in the way of tumour control and extended lifespan should be taken into consideration here. It can require an inpatient stay of a few weeks to deliver and for the pt to recover adequately for discharge.

(For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Some patients, even if fit enough, may not wish to consider the therapy given the interventions required which is entirely understandable as long as they have been informed/counselled appropriately on risks vs potential benefits. Patients would then need to be followed up between the cell therapy team and the melanoma team for a period of time before being handed back to their parent team (who may be the melanoma team in the treating hospital – but may also be in another institution) in a similar way to that CAR-T protocols currently work.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	There is guidance for each step of the TIL pathway that has been developed through delivery of the relevant clinical trials which will be reasonable to translate into standard clinical practice – most centres which have been involved in the studies or have experience in delivering cell therapies will have SOP for the various steps within the treatment pathways to ensure fitness to proceed to the next step within the TIL delivery process. This is a fairly time compressed situation (over the course of a few weeks at most for the majority) vs the “two year” rules that have been applied to checkpoint inhibitors and is mainly about patient safety within the overarching principle that once a pt has commenced procurement for TILs that the intention is for them to proceed through the entire process (procurement, induction chemotherapy, TIL administration, IL2 therapy). There is no additional testing per se.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The major benefit to be seen here is in the long term control of disease for a subset of patients from a single intervention who would otherwise die. This is with relatively short term side effect profile and very little in the way of long term issues reported either from the clinical trial, prior work from NIH and evolving real world practice (mainly US and Israel).
18. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes – as extensively described already in this statement – this provides a very meaningful strategy for patients who would otherwise have no significant

impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	recognised therapy options for their advanced disease, and for a subset – may provide control of disease for months/years/rest of their life. This is very different than the current situation for the point in the therapy pathway that the TIL therapy is being considered for. This is very clearly an unmet need for those 50% of pts who do not respond to checkpoint inhibition or who cannot tolerate that process due to severe (but reversible for the most part) side effects.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effects of the technology are mainly restricted to the procurement (surgery) to obtain the TILs for manufacture – this has the expected issues of pain at surgical site, healing, infection etc. The chemotherapy required before the cell product is given has the issues of requiring the patient to be admitted (often) for management of infection, fevers, and low cell counts. The cell product itself is actually well tolerated but can generate an infusion reaction and or a fever type pattern. IL2 used for cell engraftment causes fevers, shivering, cytokine release syndrome type picture, renal impairment, shortness of breath and similar which can require HDU support. The process to recover from the infusional aspect is around 3-4 weeks in most pts which is spent in hospital and can clearly affect the patient's quality of life adversely. Once this acute phase has settled – most patients will not have any longer term issues as a result of the process from evidence to date and mainly require follow up to ensure no unusual issues occur and to assess the response of their melanoma.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The trial is a reasonable reflection of current practice for the timepoint on the therapy pathway, both globally and in the UK. It was not compared to any other therapy as there is no other with a reasonable The important outcomes are overall response rate, tolerability (ie AEs), period of disease control and longer term side effects/QoL – these are described within the trial data. The overall survival at 5y is also available and is far more than would be expected if current standard of care of chemotherapy or supportive care was applied to the same patient group – who would have been expected to almost universally die before the 5y point.

	There are no AEs not covered in the trial data that have emerged that would be considered problematic overall as has been described elsewhere in this statement.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	See Q23.
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA268]?	No
23. How do data on real-world experience compare with the trial data?	With the product in question there is only early nascent RWE from countries other than UK/Europe who have licenced in advance of the MHRA/NICE submission but looks broadly comparable to date from what has been shared publicly and in personal correspondence between myself/others and treating teams (mostly in US and Israel to date). With a similar product/process produced by NIH for many years – there is case and case series data (but no trial) to show long term control without significant long term toxicity for the process. There is also a clinical trial from the Netherlands/Denmark with another similar product/process which shows similar data.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	Patients below 18 years were not included in the trial population but would have a similar disease behaviour expected in those not responding to checkpoint inhibition and therefore the same potential gain to win from the product as those over 18 – indeed most cell therapy processes have been in children prior to being evolved to adult settings – this needs consideration for (the thankfully small numbers but) seriously affected young pts with melanoma each year. Older and less fit patients may not be well enough with regard to comorbidities to tolerate this type of approach but the same would be true of equivalent chemotherapy or any other line of treatment if they would be at greater risk than possible benefit and so although noted – is not different to assessing for therapy in any setting with comorbidities. Those patients who are pregnant would not be

belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	considered suitable for this therapy and would need counselled accordingly as to their available options at the time. Those who have learning or mobility alterations would also need to be considered carefully for suitability for therapy in order to ensure it was offered wherever appropriate support for their needs could be safely added to the therapy planning and without significant excess risk to their wellbeing as a result.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

TIL therapy can induce long-lasting tumour regression/control, even in patients with metastatic melanoma refractory or having progressed after checkpoint inhibitors, reflecting potent and sustained immune activation.
Acute toxicities are mainly from lymphodepleting chemotherapy and high-dose IL-2 (cytopenias, fever, capillary leak, cytokine release); these are generally manageable with little significant long term toxicity seen.
It is a moderately complex and intense therapy which requires multimodality management of the patient in a controlled framework supported by clear pathways. This will only be possible, certainly initially, in a restricted number of selected centres.
TIL therapy reflects a significant step forward and meaningful option for patients who would otherwise be expected to die with no other impactful therapy.
Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement

Lifileucel for previously treated unresectable or metastatic melanoma [ID3863]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Susanna Daniels**
2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? ☒ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Melanoma Focus
4. Did your nominating organisation submit a submission?	**X** yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**X** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition. ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☒ I am drawing on others' experiences. Please specify how this information was gathered: **A questionnaire was created to answer the questions below and shared with trial investigators to share with their patients who had been on TILs trials. Other patient experts with TILs experience for melanoma outside of trials were also approached. Eight patient experts completed the questionnaire**
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Patients spoke of living on a knife edge and as fast as something was lined up for melanoma treatment, it had progressed and the goalposts were moved. A patient described feeling frightened for the future, wondering whether she would live to see her children grow up. 'I watched my 16 year old get thinner and weaker and wondered if the promised trial etc would happen let alone work. All this while trying to support 3 other children.' 'It's like being on the most horrifically bad rollercoaster that you just cannot get off. Your entire life has to revolve around your cancer. You have good days and bad days from a physical point of view so planning for anything is nigh pointless on impossible. Emotionally it is draining - living from scan to scan and then worrying about the results of the scan in between

	them. It is incessant. And then there's the public perception that melanoma is a good cancer to get. Having to explain to people that I am dying of skin cancer is draining especially when people think you are making it up, that it's not that serious, or that you are just being a drama queen' 'Living with stage 4 melanoma is an emotional roller coaster. Living with the side effects of treatment is challenging as well as managing mental health and the anxiety of living with a stage 4 diagnoses. Sleepless nights and upsetting thoughts are constant companions. Living in the moment, mindfulness, walking the dog, counselling, singing in choirs, wild swimming all help me with my physical and mental health.'
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	It is recognised that immunotherapy is an effective treatment, however, this is only effective in 40-50% of patients and many experience severe side effects (~60% treated with ip/nivo experience grade 3 or 4 side effects) and many live alongside life-long side effects. 'I suppose it depends where it spreads to and if it is operable. This isn't always the end though which is why the TIL therapy, in my opinion, is great. At the end of the day I'm sure most will try anything and everything offered.'
10. Is there an unmet need for patients with this condition?	It was felt that TILs treatment is ground-breaking for the NHS and save lives including people who don't have much hope or many options. While people are dying of melanoma, there is a need for as many options as possible. Patient experts talked about TILs being a beacon of hope. 'For me TILs has been a life saver. 2 years ago my body was complete shutting down with metastatic spread throughout my gut and surrounding areas. Tumours caused a blockage and sepsis requiring emergency surgery and a bowel resection. The surgeon who operated told me 'it's really bad in there'. TILs cleared 95% of my tumours before running out of steam. Had I stared the treatment earlier, I am absolutely certain that by now I would be cancer free. I would happily have it done again if I could clear the new growth.' 'Definitely. TILs saved my life so there definitely is a place! It's given me over 5 years and I lived to see my daughter get married this year. Something I didn't dare dream of.'

Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	TILs is a personalised treatment tailored to an individual patient's cancer using the patient's own immune system. It can lead to a long-term response and all that is needed is a resectable tumour which can be fairly superficial. 'Treatment is a one-off course and the response can be seen quickly.' 'It 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 when living with cancer. In my case, I do believe it has changed my entire system' 'It is really hard going and not an easy option. However if it works and gives me a better quality of life with my children then I own the TILs trial everything and more.'
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	The treatment is akin to a transplant and there is much experience in treating patients within the haematology world. Most side-effects are linked to the high dose chemotherapy treatment or the IL-2 treatment (which helps stimulate the immune system and activity of TILs in the body). 'It is not an easy process to have to undertake. I think you have to be strong physically in order to tolerate it.' 'It's harsh. The side effects although often short lived can be extreme. It leads to being immunosuppressed leaving patients vulnerable. It has to be given as an inpatient and in isolation.'
Patient population	
13. Are there any groups of patients who might benefit more or less from the	It was felt that patients would need to be fit enough for treatment, and that all patients could potentially benefit. As with all 'transplant' treatments, this treatment requires a high level of patient support, before, during and after treatment.

technology than others? If so, please describe them and explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	One patient's son was 16 when he underwent treatment. His disease is the same as others and should be available. Her son has since had the education he missed, obtained a degree and now working in a laboratory. A patient commented that despite the harshness of the treatment, she would wholeheartedly rechallenge with TILs should she have the opportunity.
Key messages	
17. In up to 5 bullet points, please summarise the key messages of your statement: • TILs treatments are personalised, singular treatment courses that are potentially curative.	

- TILs treatments are harsh whilst undertaking the treatment, however, they are not associated with adverse events, other than whilst undergoing the treatment.
- It is generally known quickly whether the treatment is effective
- Advanced melanoma patients are currently offered immunotherapy treatments, however, about 40% can live alongside their melanoma, many having suffered grade 3 or 4 adverse events and long-term side-effects..
- It provides hope and a future for advanced melanoma patients

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Jane Henderson**

2. Are you (please tick all that apply):	☐ a patient with the condition? **X** a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	Melanoma Focus
4. Did your nominating organisation submit a submission?	**X** yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**X** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐
7. How did you gather the information included in your statement? (please tick all that apply)	**X** I have personal experience of the condition. **X** I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	It is stressful to live with this condition. Melanoma is a cancer that does not go away completely. You live from scan to scan with uncertainty because it is so unpredictable and you are at high risk of it coming back anywhere in your body - it's scary. We have lived two lives, one 'normal' before melanoma then the fearful one after prognosis. You have to be forever vigilant checking lymph nodes between 3 or 6 monthly scans and you avoid sun exposure. You have to manage your fear of dying and you will never get back to normal. But mainly you have to learn strategies to stay positive even when you're sad and anxious feeling like a sitting duck. Keeping informed gives you more control. You control the things you can. It's a huge pressure to keep positive. Carer's needs go on the back burner. Your role changes from parent to researcher. You're afraid of missing any treatments in the pipeline. You juggle your life and your different roles within it, work, children, grandchildren, wife, so that you can keep searching for the next available treatment or trial. Then you

	have to support your whole family physically, emotionally, psychologically, and it's exhausting particularly when the best treatment for you isn't available in the UK or your MDT turn you down. You have to search for another team that will treat you. You educate yourself to read scientific papers so you do not miss potential treatments. You never accept no or that there are no other treatments for your child. Quality of life is affected not just by the condition itself, but by the negative, severe effects of currently available treatments. To summarise, Esther's treatments collectively (surgery, radiotherapy & systemic therapy) have impacted her quality of life, negatively, in the following ways. **Mobility** Cannot carry tea tray, bulky and heavy items, shopping bags. Cannot lift and hold items when bent or reaching out (like trays out of the oven and items from high shelves. Cannot look over shoulder satisfactory. Gets breathless from having reduced lung capacity and a compromised airway. Gets extremely breathless on stairs and up hills. Lymphoedema Could no longer write **Self-Care** Cannot wash, dry, brush or style her own hair. Cannot shave her own armpit. Need assistance getting out of bath. Cannot fasten bra. **Access to everyday activities** Cannot clean her house. Cannot cook meals for her family. Cannot do exercise classes.

	Cannot work. Cannot commit/be relied on. **Physical Pain** Acid Reflux Pain Stomach pain Joint Pain Arm Pain Muscle Pain Voicebox Pain As Esther's carer, my mobility and self-care haven't been affected. **Physical Pain** **I** do have back problems which have been exacerbated by assisting Esther with her self-care, lifting her and lifting her shopping. **Access to everyday activities** Lots of time off work caring for Esther and attending appointments and treatments with her. As I am self-employed, it has affected my income. I have had to return from holidays/cancel holidays/abandon my clinic when Esther has had immediate health issues, at my own expense. I have had to employ a locum in to carry on my business for long periods of time, when Esther has had surgery, and treatments in different cities and countries.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	They are a lot better than they used to be. Esther has had melanoma for 29 years, since she was 15 years old, and there were no treatments beyond surgery for our first 17 years and outcomes were bleak. Now we have systemic options but they can and do have severe side effects that leave patients with chronic health issues – even after they've failed the treatments. Your quality of life can go downhill yet the treatment hasn't worked. Targeted, immunotherapy,radiotherapy, surgery did not work for us. They were not curative and left us with permanent life changing side effects. The positives of the NHS have been the support of our oncologist who has been exceptional in her care for Esther. She allows Esther to come in before clinic starts for scan results to alleviate her high anxiety and extends our appointment time. Our SCNS' are personally invested and are there if we need them. Our radiation oncologist who made sure that the radiotherapy to Esther's arm could take place in our very limited window between the harvesting and transplant visits to Israel. The skilful phlebotomists who take their time because Esther's veins are not found easily and the kindness of the reception staff who know her by name at Weston Park Hospital in Sheffield. We have been blessed with some skilful surgeons who have taken the time to reassure and alleviate our fears. Over the last 29 years Esther, on several occasions, has been let down by the care of the NHS.. Esther's changed mole was misdiagnosed by our GP. We went back 6 months later after it continued to change. The GP reluctantly referred which took another 4 months. In 1996 her suspicious scalp lesion was excised and pathology reported it as an innocent Spitz Nevus. In 2005 a lump in her parotid gland was surgically removed. She had Stage 3 melanoma . The 1996 slide was recalled. It was melanoma in 1996. This diagnosis caused massive health anxiety. She had panic attacks at work and had to give her job up after her neck surgery as she could not fulfil her duties. She had just bought her first house, had a mortgage and no means to pay this. Major money worries on top of the anxiety of not surviving. She had a radical neck dissection on 20 December 2005 and we could not envisage life past Christmas. The neck surgery was 10 hours long and she was left with her bottom jaw swinging round to the right and could not open her mouth to eat food. There was no provision of physio for 12 weeks but she did have speech therapy. The neck surgery severed the nerve to her shoulder muscle causing shoulder drop and

	limited mobility to her dominant left arm. The sternocleinomastoid muscle on her left side was removed leaving her neck with limited movement and strength. The parotid gland was also removed in this surgery, causing fluid to seep out of her face and neck when eating. She is very self conscious of this now and it affects dining out. In 2009, after a short period of no recurrence, Esther gave birth. Sadly she had progressed to stage 4 during pregnancy. The CT scan showed 2 tumours in her right lung. We were told that if the subsequent PET scan proved melanoma to be anywhere else, she wouldn't be offered surgery and there were no systemic treatments. We asked our oncologist if there was anything that she knew of that could halt the melanoma and she said that Steven Rosenberg was pioneering a treatment called TILs in the USA. Finding out about TILs is the singular thing during all these years, that has given us hope of a future. Returning home, we were very low. Esther, then aged 28, climbed on my knee for me to comfort her, our only option, surgery, was now to be determined by the PET scan. Our oncologist had recommended that Esther's placenta be tested due to melanoma being one of the very few cancers that can cross the placenta to the baby. Staff failed to do this so the baby had to be under the care of a paediatric oncologist for the first 3 years of her life. This was an extra huge worry and trauma for Esther and the whole family. The progression of Esther's melanoma meant she would not be having any more children, no siblings for her daughter. This has been a hard issue to come to terms with, but the real risks of melanoma crossing to a foetus were too great and the lowered immunity for Esther in another pregnancy could cause further progression. In Feb 2010, Esther had a partial lung resection by a magnificent surgeon who opted for open thoracotomy so that he could feel for tumours with his hands. He found another 2 that he said felt like grains of rice (4 in total). This surgery meant Esther was unable to lift and care for her newborn for 3 months. She had to cease breastfeeding her baby which was devastating for Esther as this was an important bonding time with the baby. Esther's friends and family had to draw up a rota to care for Esther and the baby everyday for those 3 months.

	This lung surgery has caused Esther to become breathless due to the reduced lung capacity. It also caused acid reflux which made Esther dependant on PPI's. A cholecystectomy in 2013, after a tumour was detected inside the gall bladder has resulted in Esther having to take a colestyramine medication for life to bind the bile and stop salt malabsorption diarrhoea. In 2016 she had a cutaneous recurrence that was misdiagnosed as fat necrosis despite a needle biopsy. This mass continued to grow, so in 2018 the mass was removed and found to be a melanoma metastasis encased in fat necrosis. It's really difficult now to trust an ultrasound or needle biopsy and struggle to believe any benign diagnoses given the multiple misdiagnoses she has had. Throughout, we've constantly explored any potential trial options particularly TILs. We have never been eligible due to the timing of the trial and the strict inclusion/exclusion criteria. We explored the TILs trial in 2022 but we did not meet the criteria because we were treatment naïve. In 2024 we didn't meet the criteria of the next phase of the trial as we now needed to be treatment naïve and we had failed systemic therapy over the last 2 years. In 2020 Esther had a recurrence in her pancreatic head node. The MDT decided not to offer her any treatment due to her previous multi occurrences. At home that evening I was on my knees on the floor howling. I didn't know what to do. We had to source treatment ourselves, in lockdown, which took weeks. We approached the QE Birmingham. Their MDT offered a pancreaticoduodenectomy which we were accepting. Then my son found out about the MRIdian. SABR - a focused high intensity treatment that stops and starts as you breathe and protects the structures around the pancreas. This is available in many countries but not the UK unless sourced privately at a cost of £37,500. Our oncologist was very supportive responding straight away, sending medical records and scans to wherever we requested. We stayed in Oxford for two weeks to access this and it worked. Nov 2021, she had surgery to remove recurrence in her left axilla and her left bicep. Half of the left bicep was removed without clearance. This surgery caused Esther to lose lots more strength from her dominant arm. A left axillary dissection has caused lymphodema in this limb causing her pain and swelling and

	made her arm unusable. She had to change her car to an automatic as changing gear exacerbated the pain in this limb. She has reoccurring episodes of cellulitis in this limb and she has had to take long courses of antibiotics which have damaged her gut microbiome. Recent evidence shows a poor gut microbiome has a negative effect on the immune system and melanoma treatments. Esther can no longer wear her wedding, engagement and eternity rings due to the lymphodema. Her hand is different sizes at different times. In early 2022, the pre-Dab/Tram scans showed recurrence in the left supra-clavicular area and axilla. The surgeon had only gone to level 2 on the previous axilla dissection so surgery had to be repeated. During this surgery, the vagus nerve was severed causing left vocal cord paralysis. The team in Sheffield said she was to eat a solely puréed diet as they couldn't give her the barium swallow scan to check her swallow for over 10 weeks. So again, we had to access this privately, which we did within 3 days. Thankfully this showed that although her swallow is somewhat unstable, she is ok to eat solid foods albeit carefully, without it entering her windpipe. The vocal cord paralysis has caused her to experience shortness of breath when walking uphill, upstairs or exerting herself. Due to this paralysis, Esther has been left with a harsh voice, that tires easily, is very quiet and can no longer be projected. She cannot speak properly and sometimes is not understood by others, particularly when speaking on the phone. Esther is in a choir and this paralysis has been detrimental to her singing. As a soprano, she is no longer able to hold notes as air escapes where the cords do not meet, trying to hit high notes irritates her vocal cord and sends her into a coughing fit. She has lost her singing voice. Following this surgery, Esther started on Dab/Tram adjuvantly for a year. The NHS turned her down for this as she was stage 4, so again we accessed treatment privately. She tolerated this treatment well, although it did cause her to experience a severely dry mouth and throat and unfortunately she is still affected by this.

	After the standard protocol of one year of adjuvant Dab/Tram, this treatment ended. Within months, Esther had further recurrence (in her abdomen, left axilla, left bicep and clavicle). She started on Ipi/Nivo infusions in August 2023. Within 9 days of her first treatment, she noticed a mass in her neck, we determined that it was in fact a goiter and her thyroid was failing. Her thyroid had gone into overdrive and needed to get to the point where it burnt out. Once this happened Esther suffered increased fatigue, weight gain, joint pain and hair loss. Her thyroid was now under active and she needs to take Levothyroxine for the rest of her life. The joint pain continues. She proceeded with the second dose of Ipi/Nivo and after a week she started with severe colitis so the treatment was halted. For the next 6 months, she experienced extreme diarrhoea – unable to leave the vicinity of the toilet , having explosions of blood. She was hospitalised 3 times, given high dose steroids (both orally and intravenously), causing more stress because evidence shows steroid use inactivates T-cells. Antibiotics given during steroid-use caused a severe allergic skin reaction that itself required Esther to be hospitalised for. This terrible 6 month long situation had pushed Esther to the height of anxiety and the low of depression. She became so scared and obsessed, that she collected every bowel motion in tubs to examine the consistency of the faeces, and cross-reference it to the Bristol Stool chart, photographing her faecal samples and keeping a stool diary, dominating her conversation with everybody she spoke to. March 2024, she began singular Nivolumab. After 3 months, scans confirmed our suspicions that it was not working. The tumours in her axilla and bicep were visibly getting bigger and Esther had started experiencing severe sensory and mobility issues with her left arm and hand due to the extreme nerve impingement the bicep tumour was causing around the brachial plexus. This being Esther's dominant hand, she could no longer write, cut up her food, wipe her bottom, fasten her bra, button up her trousers, nor had any strength in the arm to even carry a cup of tea. She had to wear a sling as the arm was so painful and heavy given it was a 10cm tumour. In July 2024 we accessed TILs in Tel Aviv whilst Chris my son in law kept the fundraising going at home.

	During the TILs process, in between harvest and TILs infusion, Esther had a 10 day course of radiotherapy to her left axilla and bicep in the hope of reducing the tumour size to relieve some of the nerve impingement. This radiotherapy caused major skin burns and scarring.
10. Is there an unmet need for patients with this condition?	Certainly. We need a treatment for advanced and for resistant melanoma. We need access to effective treatments and we need to identify patients with a poor prognosis and treatment resistance to improve outcomes for patients. The cheapest TILs currently is in Israel. We accessed the treatment in Tel Aviv in July and August 2024 and had to fundraise to meet the £120,000 cost. We were under armed guard at Sheba Hospital – the wounded Israeli soldiers were treated here. We witnessed air missiles overhead and frequent sirens. This treatment is desperately needed in the UK. Our unmet need became apparent when our MDT team declined treatment. Many recurrences indicated we had an 'expiration date' so we're not a priority.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	There is a potential for cure with TILs therapy it is personalised tailored medicine which has been highly effective in treating advanced melanoma when other treatments have failed. It is a one time treatment with no lasting side effects compared to the potential adverse events of current treatments, which can be a lifetime of costs to the NHS and a lower quality of life for the patient. Some patients I know personally have been disease free after 10 years. TILs has reversed some of the damage other treatments have caused. She no longer needs PPi's and she has feeling and movement in her left arm. The success of the treatment has motivated Esther to become a volunteer Doula. Heidi her daughter was now able to concentrate on her studies, pass her GCSE's and start college after struggling at last years exams when her mum would have died without TILs treatment. Esther's response to TILs therapy enabled us to re-engage with living. Now we were moving forward and no longer fearful and desperate so we had to put the fundraising behind us. We stopped £18000 short of the cost. TILs gave us back our immediate future and the hope of a much longer life ahead of us. Part of this newfound ease has enabled us to travel and appreciate our own and other wonderful countries and

	cultures. Between us we have travelled to Italy, Poland, Greece, Florida, New York, not forgetting Bridlington and the beautiful Yorkshire Dales.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	It isn't available to everyone- if you have brain mets you are ruled out. You can't be on steroids. They inactivate T cells. You have to have an accessible tumour over 1.5 cm. It can be logistically challenging it needs specialised centres and a highly experienced team. In a late stage patient the time factor between harvesting & transplantation can be hard to meet. Short term lymphodepletion and IL2 induce severe short term side effects. It's harsh and the patient has to be fit to tolerate the chills , fever, nausea, oedema, breathlessness, diarrhoea and low BP as the white cells and platelets deplete. You are isolated due to Neutropenia. Neutrophils drop to under 200/ cu mm. They should be 1500/ cu mm.
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Advanced unresectable melanoma patients who have failed all possible treatments. All stage 4 patients with an accessible tumour and good organ function. Patients with active brain mets may not benefit. Patients who are too ill to tolerate TILs. Patients with a high tumour burden due to the safety risks of the treatment timeline. Patients with autoimmune disease or on high doses of steroids.

Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Access. The geographical location of the specialised centre. Patient selection. You are ruled out if you are not physically strong enough. Cost. Its expensive if you self fund.
Other issues	
15. Are there any other issues that you would like the committee to consider?	TILs has long lasting effects with the potential to be curative. Currently patients have to self fund and travel to Israel or the USA. But Israel is the only option cost wise. The war continues to escalate and security and travel are a major concern. Other treatments have lasting debilitating side effects. It's vital for heavily pretreated patients with no other options available to them. TILs therapy needs to be integrated before it is limited by progression. After TILs there is less physical pain and panic about the future. Improved mood and less anxiety. You become more self reliant. There is more joy in all our lives watching my daughter regain her health. There is less worry for the immediate future.

Key messages
17. In up to 5 bullet points, please summarise the key messages of your statement • Other treatments have severe side effects leaving patients with chronic health conditions. Quality of life deteriorates. • It's a one time personally tailored treatment without lasting adverse events. • It can have long term benefits. It is potentially curative. It offers a future for advanced patients. • It boosts your immune system to continually fight melanoma and targets many cancer antigens. • We need to bring TILs therapy to more patients like Esther, improve survival rates and help patients not die sooner.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

Lifileucel for previously treated unresectable or metastatic melanoma [ID3863]

External Assessment Group report

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Aline Navega Biz led the assessment. Emily Pulsford critiqued the company's search strategy. Abdullah Pandor summarised and critiqued the clinical effectiveness data reported within the company's submission. George Daly and Sarah Ren critiqued the statistical aspects of the submission. Aline Navega Biz, Paul Tappenden and Andrew Rawdin critiqued the health economic analysis submitted by the company and conducted additional exploratory analyses. All authors were involved in drafting and commenting on the final report.

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ABBREVIATIONS

1L	First-line
2L	Second-line
3L	Third-line
AE	Adverse event
AFT	Accelerated failure time
AIC	Akaike Information Criterion
ALL	Acute lymphoblastic leukaemia
AML	Acute myeloid leukaemia
AS	Absolute shortfall
ASA	Additional sensitivity analysis
ASCO	American Society of Clinical Oncology
ATMP	Advanced Therapy Medicinal Product
BIC	Bayesian Information Criterion
BMI	Body mass index
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
CAR-T	Chimeric antigen receptor T-cell
CC	Complications and comorbidity
CDSR	Cochrane Database of Systematic Reviews
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CMU	Commercial Medicines Unit
CR	Complete response
CRD	Centre for Reviews and Dissemination
CS	Company's submission
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte associated protein 4
DALY	Disability-adjusted life year
DARE	Database of Abstracts of Reviews of Effects
DCO	Data cut-off
DCR	Disease control rate
DM	Decision modifier
DoR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EA	Exploratory analysis
EAG	External Assessment Group
ECOG	Eastern Cooperative Oncology Group
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool

EoL	End-of-life
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire
EQ-5D	Euroqol 5-Dimensions
EQ-5D-3L	Euroqol 5-Dimensions 3-Level
EQ-5D-5L	Euroqol 5-Dimensions 5-Level
FAS	Full Analysis Set
FDA	Food and Drug Administration
GP	General Practitioner
HCRU	Health care resource use
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
HTAi	Health Technology Assessment International
HUI-2	Health Utilities Index Mark 2
ICER	Incremental cost-effectiveness ratio
ICI	Immune checkpoint inhibitor
ICU	Intensive care unit
IL-2	Interleukin-2
INV	Investigator
IPD	Individual patient data
IRC	Independent Review Committee
ISPOR	The Professional Society for Health Economics and Outcomes Research
ITC	Indirect treatment comparison
IV	Intravenous
KM	Kaplan-Meier
KOL	Key opinion leader
LD	Lymphodepletion
LDH	Lactate dehydrogenase
LoT	Line of treatment
LYG	Life year gained
MAIC	Matching-adjusted indirect comparison
MAPK	Mitogen-activated protein kinase
MCM	Mixture-cure model
MEK	Mitogen-activated protein kinase
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic resonance imaging
N/a	Not applicable
NCCN	National Comprehensive Cancer Network
NG	NICE Guideline
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NHSCII	NHS Cost Inflation Index
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMA-LD	Non-myeloablative lymphodepletion
NR	Not reported

ONS	Office for National Statistics
ORR	Objective response rate
OS	Overall survival
PAS	Patient Access Scheme
PD	Progressed disease
PD-1	Programmed death 1
PDAwCS	Pooled Data Aligned with Commercial Specifications
PD-L1	Programmed death ligand 1
PET	Positron emission tomography
PF	Progression-free
PFS	Progression-free survival
PH	Proportional hazards
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PS	Performance status *or* proportional shortfall
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QQ	Quantile-quantile
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria In Solid Tumors
RoB 2	Risk of Bias version 2
SAS	Safety Analysis Set
SD	Stable disease *or* standard deviation
SEER	Surveillance, Epidemiology, and End Results
SF-36	Short Form 36
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SMR	Standardised mortality ratio
STC	Simulated treatment comparison
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TH	Tumour harvest
TIL	Tumour infiltrating lymphocytes
TNM	Tumour, node, metastasis
TPS	Tumour proportion score
TSD	Technical Support Document
T-VEC	Talimogene laherparepvec
UK	United Kingdom
USA	United States of America
UV	Ultraviolet
VAS	Visual analogue scale
WHO-ICTRP	World Health Organisation International Clinical Trials Registry Platform
WTP	Willingness-to-pay

1. EXECUTIVE SUMMARY

This report assesses lifileucel for the treatment of [redacted]. This executive summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision-making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 outlines the key model outcomes and the modelling assumptions that have the greatest impact on the ICER. Sections 1.3 to 1.5 summarise the decision problem, the clinical evidence and the company's economic model and explain the key issues in more detail. The results of the EAG's preferred analyses and additional sensitivity analyses are summarised in Section 1.6. Background information on the condition, technology and evidence and information on non-key issues is detailed in the main EAG report.

All issues identified represent the EAG's view, not necessarily the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

The company's submission (CS) includes a systematic literature review (SLR) of studies reporting on the clinical efficacy and safety of lifileucel in previously treated patients with unresectable or metastatic melanoma. The SLR identified one relevant single-arm study of lifileucel – Study C-144-01 – which reports on clinical outcomes for adult patients (≥18 years) with unresectable or metastatic melanoma (stage IIIC or stage IV) who received the lifileucel infusion after having progressed following treatment on at least one systemic therapy, including a PD-1 blocking antibody, and if BRAF V600 mutation-positive, a BRAF inhibitor or BRAF inhibitor in combination with a mitogen-activated protein kinase (MEK) inhibitor. The company's economic model assesses the cost-effectiveness of lifileucel versus ipilimumab, chemotherapy and best supportive care (BSC) in patients with previously treated advanced melanoma based on unanchored indirect treatment comparisons (ITCs) of Study C-144-01 and external data from studies of ipilimumab and chemotherapy (da Silva *et al.* and Mangin *et al.*). The key issues identified by the EAG are summarised in Table 1.

Table 1: Summary of the EAG's key issues

ID6405	Summary of issue	Report sections
Issue 1	Uncertainty around the relative and absolute treatment effects for lifileucel versus ipilimumab	4.5 and 5.3.5 (critical appraisal points 2 and 3)
Issue 2	Uncertainty around the relative treatment effects for lifileucel versus BSC	5.3.5 (critical appraisal point 6)
Issue 3	Uncertainty around the outcomes for patients who do not receive the within-specification lifileucel infusion	5.3.5 (critical appraisal point 5)
Issue 4	Concerns regarding the company's selection of MCMs for lifileucel	5.3.5 (critical appraisal point 3)
Issue 5	Uncertainty around the utility values used in the company's model	5.3.5 (critical appraisal point 7)
Issue 6	Inappropriate inclusion of the higher decision modifier for the comparison against ipilimumab	5.3.5 (critical appraisal point 9)
Issue 7	Uncertainty around the costs of set-up, logistics, training and delivery of lifileucel	5.3.5 (critical appraisal point 8)

EAG - External Assessment Group; BSC - best supportive care; MCM - mixture-cure model

The key differences between the company's original base case model and the EAG's preferred analysis are as follows:

(i) *Modelling the effects of lifileucel versus ipilimumab:* The company's model uplifts the mixture-cure models (MCMs) for progression-free survival (PFS) and overall survival (OS) in the lifileucel group based on data from Study C-144-01 by the ratio of the simulated treatment comparison (STC) adjusted and unadjusted hazard ratios (HRs) to estimate absolute lifileucel outcomes in the da Silva ipilimumab population. Outcomes for ipilimumab are based on standard parametric survival models fitted directly to reconstructed pseudo individual patient data (IPD) from da Silva *et al*. The EAG's analysis applies the unadjusted MCMs based on Study C-144-01 in the lifileucel group and estimates outcomes for the ipilimumab group by applying the inverse HRs from the STC to the lifileucel MCMs for PFS and OS.

(ii) *Modelling the effects of lifileucel versus BSC:* The company's model applies an HR of 2.0 to the PFS and OS models for chemotherapy to estimate outcomes for BSC, based on a structured elicitation exercise conducted with clinical experts. The EAG's preferred analysis assumes that there is no difference in outcomes between chemotherapy and BSC (i.e., chemotherapy confers no additional treatment effect over BSC).

(iii) *Use of alternative MCMs for lifileucel:* The company's model applies a log-normal MCM for lifileucel PFS and an exponential MCM for lifileucel OS. The EAG's preferred analysis applies log-logistic MCMs in the lifileucel group for both endpoints.

(iv) *Cure time point:* The company's model assumes that lifileucel- and ipilimumab-treated patients who remain alive and progression-free at 3 years: (a) rebound to a level of health-related quality of life (HRQoL) equivalent to that of the general population and (b) require no further clinical follow-up after this time point. The EAG's preferred model moves this time point to 5 years.

(v) *Lifileucel administration costs.* The company's model applies administration costs based on NHS Reference Costs and excludes additional costs relating to the set-up, implementation, logistics and delivery of lifileucel. Following advice from NHS England, the EAG's preferred analysis includes the NHS England 2025/26 chimeric antigen receptor T-cell (CAR-T) tariff cost of [redacted] for patients who receive the lifileucel infusion.

The EAG's model also includes other minor amendments including the correction of model errors and the alternative weighting of tumour procurement costs for patients in whom the lifileucel infusion is planned.

1.2 Overview of the key model outcomes

NICE technology appraisals (TAs) compare how much a new technology improves length of life (OS) and HRQoL in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Compared with ipilimumab, chemotherapy and BSC, the company's model indicates that lifileucel impacts on QALYs by:

- Extending PFS, including the potential for cure in a proportion of patients
- Extending OS, including the potential for cure in a proportion of patients
- Slightly increasing QALY losses associated with adverse events (AEs).

The company's model suggests that lifileucel impacts on costs by:

- Increasing drug costs due to the acquisition and administration costs associated with the lifileucel regimen (including tumour procurement, lymphodepletion (LD) chemotherapy, the lifileucel infusion and post-infusion interleukin-2 [IL-2]).
- Increasing health state costs as a consequence of extended OS.
- Slightly increasing the expected costs of managing AEs.

The modelling assumptions that have the greatest effect on the ICER are:

- The approach used to model the relative and absolute effects of lifileucel versus ipilimumab
- The decision modifier applied to the comparison of lifileucel versus ipilimumab
- The MCMs for lifileucel PFS and OS
- The inclusion of the NHS England CAR-T tariff for people who receive the lifileucel infusion
- The use of non-Reference Case discount rates of 1.5% for health outcomes and costs.

1.3 The decision problem: Summary of the EAG's key issues

The company's proposed positioning of lifileucel is in line with its anticipated marketing authorisation, that is, for:

[redacted]

The decision problem addressed in the CS is generally in line with the final NICE scope. The company's ITCs compare lifileucel against ipilimumab and chemotherapy and the company's economic model compares lifileucel against ipilimumab, chemotherapy and BSC. Whilst the NICE scope lists individual chemotherapy regimens, the company's economic model instead considers chemotherapy as a basket of therapies. The company's clarification response states that ipilimumab monotherapy is the main comparator for lifileucel. However, the EAG's clinical advisors commented that most patients who are able to receive ipilimumab will have already done so in the first-line setting (in combination with nivolumab) and that chemotherapy is not commonly used due to its limited effectiveness. As such, the EAG believes that BSC may be the main comparator for lifileucel.

1.4 The clinical effectiveness evidence: Summary of the EAG's key issues

The CS presents data from one pivotal, single-arm study (C-144-01) evaluating lifileucel in adults (≥18 years) with stage IIIC or IV melanoma who had progressed after at least one prior systemic therapy, including a PD-1 inhibitor and, if BRAF V600 mutation-positive, a BRAF inhibitor (with or without a MEK inhibitor). The CS focuses only on patients who received cryopreserved lifileucel (generation 2) meeting manufacturing product specifications (Cohorts 2 and 4). Patients underwent a three-step treatment regimen comprising LD chemotherapy (cyclophosphamide and fludarabine), a single lifileucel infusion, and high-dose IL-2 administration (up to six doses). Multiple analysis sets were presented. The Full Analysis Set (FAS) included 153 patients (87 from Cohort 4, 66 from Cohort 2), excluding those who received an out-of-specification infusion. The Pooled Data Aligned with Commercial Specifications (PDAwCS) efficacy set included [redacted] who received lifileucel within the proposed Summary of Product Characteristics (SmPC) dosing range and manufactured at facilities approved for commercial supply. This dataset formed the basis for the results used in the company's economic model. As of the 30th June 2023 data cut-off (DCO) (median follow-up = [redacted]), pooled results from Cohorts 2 and 4 (PDAwCS efficacy set) demonstrated an objective response rate (ORR) of [redacted], as assessed by an Independent Review Committee (IRC) using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria. Complete response (CR) was achieved in [redacted], partial response (PR) in [redacted] and stable disease (SD) was observed in [redacted] patients. Median PFS, as assessed by the IRC, was [redacted], with a 1-year PFS rate of [redacted] and a 4-year PFS rate of [redacted]. Median OS, as assessed by the investigators, was

[redacted] with a 12-month OS rate of [redacted]. All patients in the Safety Analysis Set (SAS) (N=156) experienced ≥1 treatment-emergent adverse events (TEAEs) of any grade during the course of the study. The most common TEAEs with an incidence of 20% or higher (any grade) included: [redacted] The most common Grade 3/4 AEs included: [redacted] Six deaths occurred within 30 days after infusion, four of which were attributed to AEs and two to progressive disease.

Due to the absence of head-to-head randomised studies, the company undertook ITCs comparing lifileucel versus ipilimumab and lifileucel versus chemotherapy. The company conducted an STC for the comparison of lifileucel versus ipilimumab, with da Silva *et al.* (N=162) informing outcomes for ipilimumab. The adjusted HRs were estimated to be [redacted] suggesting a larger clinical benefit compared to the unadjusted HRs of [redacted]. For the comparison of lifileucel versus chemotherapy, an unadjusted ITC analysis was presented, with Mangin *et al.* (N=50) informing outcomes for chemotherapy. The (naïve) unadjusted HRs were estimated to be [redacted].

The uncertainties around the relative effectiveness of lifileucel versus its comparators impact directly on the company's economic model. These issues are described in Section 1.5.

1.5 The cost-effectiveness evidence: Summary of the EAG's key issues

The company's model assesses the cost-effectiveness of lifileucel versus ipilimumab, chemotherapy and BSC for the treatment of [redacted] The model uses a partitioned survival approach for patients receiving the lifileucel infusion, with a preceding decision tree which is used to account for costs and outcomes accrued by patients for whom the lifileucel infusion is received within-specification or not (either the patient receives an out-of-specification infusion, or discontinues or dies prior to receiving the infusion). The partitioned survival model includes three health

states: (i) progression-free (PF), (ii) progressed disease (PD), and (iii) dead. The model evaluates the cost-effectiveness of lifileucel versus its comparators from an NHS and Personal Social Services (PSS) perspective over a [redacted]-year (lifetime) horizon. Caregiver effects are not included. Health outcomes and costs are discounted at a rate of 3.5% per annum in the base case analysis.

PFS and OS for patients who receive the lifileucel infusion are modelled using MCMs fitted to data from the PDAwCS efficacy set in Study C-144-01. PFS and OS for ipilimumab are modelled using standard parametric survival models fitted to data from da Silva *et al.* PFS and OS for chemotherapy are modelled using standard parametric survival models fitted to data from Mangin *et al.* Outcomes for BSC are modelled by applying an HR of 2.0 to the chemotherapy survival models. For the economic comparison of lifileucel versus ipilimumab, the lifileucel MCMs are raised to the power of the ratio of the STC-adjusted and unadjusted HRs from the company's ITC; the other comparisons do not involve adjusting the lifileucel MCMs as they are informed by naïve ITCs. Health state utility values are modelled using unweighted means of utility values reported in published literature and previous NICE TAs. The model assumes that lifileucel- and ipilimumab-treated patients who remain alive and progression-free at 3 years rebound to general population HRQoL. The model includes costs associated with: (i) drug acquisition and administration (including tumour procurement and pre- and post-infusion treatments for patients in the lifileucel group); (ii) health state management (scans, tests and clinic visits); (iii) the management of AEs and (iv) end-of-life care costs. Cost-effectiveness results are reported as pairwise comparisons; fully incremental analyses are not presented in the CS.

The list price for the lifileucel infusion is [redacted]. The company has proposed a Patient Access Scheme (PAS) which takes the form of a simple price discount of [redacted]. The price of the infusion including the PAS is [redacted]. The company's original model base case model results including the PAS are as follows:

- *Lifileucel versus ipilimumab (STC-adjusted comparison).* Including a decision modifier of 1.7, the probabilistic version of the model suggests that the ICER for lifileucel versus ipilimumab is expected to be [redacted] per QALY gained. The deterministic ICER is higher at [redacted] per QALY gained.
- *Lifileucel versus chemotherapy (naïve ITC).* Including a decision modifier of 1.7, the probabilistic version of the model suggests that the ICER for lifileucel versus chemotherapy is expected to be [redacted] per QALY gained. The deterministic ICER is higher at [redacted] per QALY gained.
- *Lifileucel versus BSC (naïve ITC).* Including a decision modifier of 1.7, the probabilistic version of the model suggests that the ICER for lifileucel versus BSC is expected to be [redacted] per QALY gained. The deterministic ICER is higher at [redacted] per QALY gained.

Following the clarification round, the company submitted a revised model. The probabilistic version of the revised model suggests pairwise ICERs for lifileucel versus ipilimumab, chemotherapy and BSC of [redacted], [redacted] and [redacted] per QALY gained, respectively. The corresponding ICERs based on the deterministic version of the model are higher at [redacted], [redacted] and [redacted] per QALY gained.

The EAG's critical appraisal identified several issues relating to the company's model, including: uncertainty around the approach used to model relative and absolute outcomes for lifileucel, ipilimumab and BSC (Issue 1 and Issue 2); uncertainty around the outcomes for patients who do not receive the within-specification lifileucel infusion (Issue 3); concerns regarding the MCMs for lifileucel selected by the company (Issue 4); uncertainty around the health state utility values (Issue 5); the use of an inappropriate decision modifier for the comparison against ipilimumab (Issue 6) and concerns relating to the exclusion of costs of set-up, logistics and training and delivery of lifileucel (Issue 7).

Issue 1: Uncertainty around the relative and absolute treatment effects for lifileucel versus ipilimumab

Report section	4.5 and 5.3.5 (critical appraisal points 2 and 3)
Description of issue and why the EAG has identified it as important	The company estimated the relative effectiveness of lifileucel versus ipilimumab using an unanchored STC. The economic model applies the ratio of STC-adjusted and unadjusted HRs to the lifileucel MCMs for PFS and OS to estimate absolute outcomes for lifileucel-treated patients in the da Silva ipilimumab population. The EAG notes the following issues regarding the company's approach: • The EAG has concerns regarding the robustness of the STC results as they are largely affected by adjusting for the difference in lactate dehydrogenase (LDH) levels, while the adjustment of other observed covariates has only a limited impact on the results. Given concerns regarding the covariates included for adjustment, the potential residual bias due to unobserved confounders, and the lack of sufficient evidence supporting the assessment of the model assumptions, the EAG considers that the STC-adjusted results should be interpreted with caution. • Applying the ratio of STC-adjusted and unadjusted HRs lifts the lifileucel MCM survivor functions and results in higher implied cure fractions than those estimated using the Study C-144-01 data (implied cure fraction for PFS = [redacted]; implied cure fraction for OS = [redacted]). These implied cure fractions after adjustment far exceed clinical expectations for lifileucel (estimated to be [redacted] by clinical experts consulted by the company). • The clinical experts consulted by the company and the EAG commented that a plateau would be expected for ipilimumab, indicating long-term survival for a proportion of patients. However, owing to the short follow-up duration in the da Silva study, the company only fitted standard parametric survival models to the PFS and OS data for ipilimumab. The model assumes that [redacted] of ipilimumab-treated patients are cured for OS, but no patients are cured for PFS. Including this cure assumption has a negligible impact on mean OS in the ipilimumab group (mean OS including cure assumption = 1.322 years; mean OS excluding cure assumption = 1.321 years). As such, the EAG considers that the company's model does not fully reflect the possibility of cure in ipilimumab-treated patients.

What alternative approach has the EAG suggested?	The EAG prefers: (a) to apply the unadjusted MCMs for PFS and OS in the lifileucel group and (b) to apply the inverse of the STC-adjusted HRs to these models to estimate outcomes for the ipilimumab group. Taken together, this approach results in PFS and OS outcomes for lifileucel which reflect the available data from Study C-144-01 and which reflect clinical expectations of cure for a small proportion of ipilimumab-treated patients.
What is the expected effect on the cost-effectiveness estimates?	Based on the EAG's analysis which includes error corrections (Exploratory Analysis [EA] 1), the application of the inverse STC-adjusted HR to the unadjusted lifileucel MCMs increases the ICER for lifileucel versus ipilimumab from [redacted] to [redacted] per QALY gained (EA2). As expected, the impact of this alternative approach on the ICER against the other comparators is limited (<£1,000).
What additional evidence or analyses might help to resolve this key issue?	The EAG believes that this alternative approach results in model-predicted outcomes for the lifileucel and ipilimumab groups which are better aligned with clinical expectations compared with the company's base case model. However, further clinical input may be warranted.

Issue 2: Uncertainty around the relative treatment effects for lifileucel versus BSC

Report section	5.3.5 (critical appraisal point 6)
Description of issue and why the EAG has identified it as important	The company's SLR did not identify any studies which report on PFS or OS for patients receiving BSC. The company's model assumes that the hazards of progression and death for patients receiving BSC are twice as high as those for patients receiving chemotherapy. This assumption was based on a structured elicitation exercise undertaken during an advisory board meeting with clinical experts which was held by the company. However, the minutes of the meeting state that an unspecified number of clinicians considered that *"chemotherapy was about the same as giving no treatment (i.e., no treatment effect)."* The EAG's clinical advisors agreed with this view.
What alternative approach has the EAG suggested?	The EAG's preferred analysis applies an HR of 1.0 to the chemotherapy models to estimate BSC outcomes. The company's assumption of an HR of 2.0 is applied in the EAG's additional sensitivity analyses (ASAs).
What is the expected effect on the cost-effectiveness estimates?	Applying an HR for BSC versus chemotherapy of 1.0 has a small impact on the ICERs for lifileucel versus ipilimumab and versus chemotherapy, but a more pronounced impact on the ICER versus BSC. Based on the EAG's corrected model (EA1), this analysis (EA3) increases the ICER for lifileucel versus BSC from [redacted] to [redacted] per QALY gained, and decreases the ICERs for lifileucel versus ipilimumab from [redacted] to [redacted] per QALY gained, and lifileucel versus chemotherapy from [redacted] to [redacted] per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	Further clinical opinion may be useful to determine the most plausible outcomes for patients receiving BSC alone.

Issue 3: Uncertainty around the outcomes for patients who do not receive the within-specification lifileucel infusion

Report section	5.3.5 (critical appraisal point 5)
Description of issue and why the EAG has identified it as important	The company's model assumes that amongst the population of patients in whom the lifileucel infusion is planned, [redacted] will discontinue or die before receiving the infusion or will receive an out-of-specification infusion. Patients who discontinue or receive an out-of-specification infusion are assumed to receive one of the model comparators, with costs and outcomes based on a weighted average (ipilimumab [redacted], chemotherapy [redacted] or BSC [redacted]). The CS does not

	provide any information on the observed survival outcomes for patients in Study C-144-01 who did not receive the infusion. The EAG asked the company to provide Kaplan-Meier plots for PFS and OS for people in Cohorts 2 and 4 of Study C-144-01 who did not receive the infusion. The company stated that they were unable to provide these data within the time frame for providing responses to the clarification questions.
What alternative approach has the EAG suggested?	Providing the data on outcomes for non-infused patients in Study C-144-01.
What is the expected effect on the cost-effectiveness estimates?	Without further data, the potential impact of misrepresenting outcomes for patients who do not receive the lifileucel infusion on the ICERs is unknown.
What additional evidence or analyses might help to resolve this key issue?	The requested data on outcomes for patients who did not receive the infusion in Study C-144-01 would provide a means of determining the credibility of model-predicted OS for the overall (infused and non-infused) lifileucel group.

Issue 4: Concerns regarding the company's selection of MCMs for lifileucel

Report section	5.3.5 (critical appraisal point 3)
Description of issue and why the EAG has identified it as important	The company's base case model uses the log-normal MCM for PFS and the exponential MCM for OS in the lifileucel group. These models suggest cure fractions of [redacted] for PFS and [redacted] for OS. The log-normal MCM for PFS does not align with the preferences of the clinical experts consulted by the company. The exponential MCM for OS suggests a cure fraction which was considered by one of the clinical experts consulted by the company to be *"too high"* and leads to a [redacted] difference in the cure fractions for PFS and OS, despite the absence of further effective therapies following progression. The EAG prefers the use of alternative MCMs for lifileucel for both endpoints.
What alternative approach has the EAG suggested?	The EAG prefers the log-logistic MCM for PFS because it is the best-fitting distribution, and it aligns with the preferences of clinical experts consulted in the one-to-one meetings held by the company. The EAG prefers the log-logistic MCM for OS because it closely aligns with the expected proportion of patients achieving cure of [redacted] suggested by clinicians at the company's advisory board meeting, and applying this alternative OS MCM reduces the difference between the PFS and OS cure fraction estimates to [redacted], which the EAG considers to be more clinically plausible.
What is the expected effect on the cost-effectiveness estimates?	Based on the EAG's corrected model (EA1), the use of log-logistic MCMs for lifileucel PFS and OS (EA4) increases the ICER for lifileucel versus ipilimumab from [redacted] to [redacted] per QALY gained, the ICER for lifileucel versus chemotherapy from [redacted] to [redacted] per QALY gained, and the ICER for lifileucel versus BSC from [redacted] to [redacted] per QALY gained. The EAG's ASAs explore the impact of using all alternative fitted MCMs for lifileucel PFS and OS (see Table 2).
What additional evidence or analyses might help to resolve this key issue?	The EAG does not believe that further analyses are required to address this issue.

Issue 5: Uncertainty around the utility values used in the company's model

Report section	5.3.5 (critical appraisal point 7)

Description of issue and why the EAG has identified it as important	The health state utility values used in the company's model have been calculated based on unweighted means of utility values reported in 2 published studies and 10 TAs of treatments for advanced melanoma. The EAG considers the company's approach to be unconventional – typically, utility values applied in a model would be taken from the same clinical study used to inform outcomes, or in the absence of such data, from some individual external source which is judged to be relevant and applicable to the model health states. The EAG also notes that some of the utility values included in the unweighted means do not relate to patients at the relevant lines of therapy for the lifileucel target population (second-line [2L], or third-line if BRAF+) and some values are not based on the Euroqol 5-Dimensions 3-Level (EQ-5D-3L). In addition, the clinical experts consulted by the company stated that they expected to see a large difference in utility between the PF and PD states and this is not reflected in the values applied in the company's model.
What alternative approach has the EAG suggested?	Overall, the EAG believes that there is no single source which provides utility values which are both clinically plausible and which fully adhere to the NICE Reference Case. The EAG's preferred analysis retains the company's base case utility values; however, the EAG believes that this aspect of the model should be interpreted with caution. The EAG has conducted ASAs to explore the impact of using alternative health state utility values.
What is the expected effect on the cost-effectiveness estimates?	Relative to the EAG's preferred analysis (EA8), the use of alternative health state utility values (PF = 0.80 and PD = 0.68, ASA6) has a small impact on the ICERs for lifileucel versus all comparators, with the ICER for lifileucel versus ipilimumab decreasing from [redacted] to [redacted] per QALY gained, the ICER for lifileucel versus chemotherapy decreasing from [redacted] to [redacted] per QALY gained, and the ICER for lifileucel versus BSC decreasing from [redacted] to [redacted] per QALY gained. The EAG notes that the limited impact is partly caused by the assumption of cure at 3 years for lifileucel-treated patients. The EAG's ASAs indicate that the other utility parameters in the model are not key drivers of the ICER (see Table 2, ASA7 and ASA8).
What additional evidence or analyses might help to resolve this key issue?	Further clinical input may be useful in determining the plausibility of the utility values applied in the company's base case model. This should include consideration of the impact of disease progression on HRQoL.

Issue 6: Inappropriate inclusion of the higher decision modifier for the comparison against ipilimumab

Report section	5.3.5 (critical appraisal point 9)
Description of issue and why the EAG has identified it as important	The company's model applies a decision modifier of 1.7 to the pairwise comparisons of lifileucel versus all three comparators (ipilimumab, chemotherapy and BSC). All results presented in the CS include this decision modifier. However, based on the comparator QALYs predicted for the ipilimumab group and the patient characteristics in Study C-144-01, the York Shortfall Calculator indicates that a decision modifier of 1.2 is applicable.
What alternative approach has the EAG suggested?	Based on recommendations made in Decision Support Unit (DSU) Technical Support Document (TSD) 23, the EAG believes that a decision modifier of 1.2 should be applied for the comparison against ipilimumab and a decision modifier of 1.7 should be applied for the comparisons against chemotherapy and BSC.
What is the expected effect on the cost-effectiveness estimates?	The EAG's preferred analysis (EA8) suggests an ICER for lifileucel versus ipilimumab of [redacted] per QALY gained, based on a decision modifier of 1.2. Applying a decision modifier of 1.7 reduces the ICER to [redacted] per QALY gained (ASA12). This analysis does not impact on the comparisons against chemotherapy and BSC.

What additional evidence or analyses might help to resolve this key issue?	The EAG does not believe that further analyses are required to resolve this issue.

Issue 7: Uncertainty around the costs of set-up, logistics, training and delivery of lifileucel

Report section	5.3.5 (critical appraisal point 8)
Description of issue and why the EAG has identified it as important	The EAG has concerns that the costs reflected in the company's model may not fully reflect the costs associated with set-up, logistics, training and delivery of lifileucel. In May 2025, NHS England requested that the 2025/26 CAR-T tariff is applied to lifileucel within the company's model (tariff cost = [redacted]).
What alternative approach has the EAG suggested?	The EAG has included the NHS England tariff cost to patients who receive the lifileucel infusion (either within or outside of specifications). This is assumed to cover the costs of tumour tissue procurement, LD chemotherapy administration costs, IL-2 administration and monitoring costs, AEs, 100 days of disease management costs and all other NHS costs relating to the set-up and delivery of lifileucel.
What is the expected effect on the cost-effectiveness estimates?	Based on the EAG's analysis which includes error corrections (EA1), the inclusion of the NHS England tariff cost (EA7) increases the ICER for lifileucel versus ipilimumab from [redacted] to [redacted] per QALY gained, the ICER for lifileucel versus chemotherapy from [redacted] to [redacted] per QALY gained, and the ICER for lifileucel versus BSC from [redacted] to [redacted] per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	The EAG does not believe that further evidence or analyses are required to resolve this issue.

1.6 Summary of EAG's preferred model and sensitivity analysis results

The results of the EAG's preferred model and additional sensitivity analyses are summarised in Table 2. EA8 reflects the EAG's preferred model. Owing to unresolvable problems with the company's probabilistic sensitivity analysis (PSA), results are presented only using the deterministic versions of the model. All results presented here include the proposed PAS discount for lifileucel and the list prices for other drugs. The results of the analyses including confidential price discounts for comparators are available in a separate appendix to this EAG report.

Modelling errors identified by the EAG are described in Section 5.3.5. For further details of the exploratory analyses undertaken by the EAG, see Section 5.5.

Table 2: Summary of EAG's preferred model results (deterministic), lifileucel versus ipilimumab, chemotherapy and BSC

Scenario	Lifileucel vs ipilimumab				Lifileucel vs chemotherapy				Lifileucel vs BSC			
	Inc. QALYs	**Inc. costs**	**ICER**	**DM**	**Inc. QALYs**	**Inc. costs**	**ICER**	**DM**	**Inc. QALYs**	**Inc. costs**	**ICER**	**DM**
Company's original model	3.58	[redacted]	[redacted]	1.7	2.53	[redacted]	[redacted]	1.7	2.80	[redacted]	[redacted]	1.7
Company's updated model	3.20	[redacted]	[redacted]	1.7	2.31	[redacted]	[redacted]	1.7	2.58	[redacted]	[redacted]	1.7
EA1: Correction of errors	3.21	[redacted]	[redacted]	1.2	2.32	[redacted]	[redacted]	1.7	2.59	[redacted]	[redacted]	1.7
EA2: Application of inverse STC-adjusted HR to unadjusted lifileucel PFS and OS MCMs to estimate outcomes for ipilimumab group	1.91	[redacted]	[redacted]	1.2	2.32	[redacted]	[redacted]	1.7	2.59	[redacted]	[redacted]	1.7
EA3: Application of HR for BSC versus chemotherapy of 1.0	3.27	[redacted]	[redacted]	1.2	2.37	[redacted]	[redacted]	1.7	2.37	[redacted]	[redacted]	1.7
EA4: Use of log-logistic	2.93	[redacted]	[redacted]	1.2	2.07	[redacted]	[redacted]	1.7	2.34	[redacted]	[redacted]	1.7

Scenario	Lifileucel vs ipilimumab				Lifileucel vs chemotherapy				Lifileucel vs BSC			
	Inc. QALYs	**Inc. costs**	**ICER**	**DM**	**Inc. QALYs**	**Inc. costs**	**ICER**	**DM**	**Inc. QALYs**	**Inc. costs**	**ICER**	**DM**
MCMs for lifileucel PFS and OS												
EA5: Cure time point = 5 years	3.18	[redacted]	[redacted]	1.2	2.30	[redacted]	[redacted]	1.7	2.57	[redacted]	[redacted]	1.7
EA6: Alternative weighting of tumour procurement costs	3.21	[redacted]	[redacted]	1.2	2.32	[redacted]	[redacted]	1.7	2.59	[redacted]	[redacted]	1.7
EA7: Inclusion of NHS tariff cost	3.21	[redacted]	[redacted]	1.2	2.32	[redacted]	[redacted]	1.7	2.59	[redacted]	[redacted]	1.7
EA8: EAG preferred analysis	1.79	[redacted]	[redacted]	1.2	2.11	[redacted]	[redacted]	1.7	2.11	[redacted]	[redacted]	1.7
ASA1a: Lifiluecel PFS – exponential MCM	1.81	[redacted]	[redacted]	1.2	2.13	[redacted]	[redacted]	1.7	2.13	[redacted]	[redacted]	1.7
ASA1b: Lifileucel PFS – Weibull MCM	1.82	[redacted]	[redacted]	1.2	2.14	[redacted]	[redacted]	1.7	2.14	[redacted]	[redacted]	1.7
ASA1c: Lifiluecel PFS –	1.81	[redacted]	[redacted]	1.2	2.13	[redacted]	[redacted]	1.7	2.13	[redacted]	[redacted]	1.7

Scenario	Lifileucel vs ipilimumab				Lifileucel vs chemotherapy				Lifileucel vs BSC			
	Inc. QALYs	Inc. costs	ICER	DM	Inc. QALYs	Inc. costs	ICER	DM	Inc. QALYs	Inc. costs	ICER	DM
Gompertz MCM												
ASA1d: Lifiluecel PFS – log-logistic MCM (same as EA8)	1.79	[redacted]	[redacted]	1.2	2.11	[redacted]	[redacted]	1.7	2.11	[redacted]	[redacted]	1.7
ASA1e: Lifiluecel PFS – log-normal MCM	1.80	[redacted]	[redacted]	1.2	2.11	[redacted]	[redacted]	1.7	2.11	[redacted]	[redacted]	1.7
ASA2a: Lifiluecel OS – exponential MCM	1.94	[redacted]	[redacted]	1.2	2.36	[redacted]	[redacted]	1.7	2.36	[redacted]	[redacted]	1.7
ASA2b: Lifiluecel OS – Weibull MCM	1.95	[redacted]	[redacted]	1.2	2.38	[redacted]	[redacted]	1.7	2.38	[redacted]	[redacted]	1.7
ASA2c: Lifiluecel OS – Gompertz MCM	1.94	[redacted]	[redacted]	1.2	2.36	[redacted]	[redacted]	1.7	2.36	[redacted]	[redacted]	1.7
ASA2d: Lifiluecel OS – log-logistic MCM (same as EA8)	1.79	[redacted]	[redacted]	1.2	2.11	[redacted]	[redacted]	1.7	2.11	[redacted]	[redacted]	1.7
ASA2e: Lifiluecel OS	1.72	[redacted]	[redacted]	1.2	2.00	[redacted]	[redacted]	1.7	2.00	[redacted]	[redacted]	1.7

Scenario	Lifileucel vs ipilimumab				Lifileucel vs chemotherapy				Lifileucel vs BSC			
	Inc. QALYs	**Inc. costs**	**ICER**	**DM**	**Inc. QALYs**	**Inc. costs**	**ICER**	**DM**	**Inc. QALYs**	**Inc. costs**	**ICER**	**DM**
– log-normal MCM												
ASA2f: Lifiluecel OS – generalised gamma MCM	1.88	[redacted]	[redacted]	1.2	2.25	[redacted]	[redacted]	1.7	2.25	[redacted]	[redacted]	1.7
ASA3: Inverse unadjusted HRs from company's ITC applied to lifileucel MCMs	1.12	[redacted]	[redacted]	1.2	2.16	[redacted]	[redacted]	1.7	2.16	[redacted]	[redacted]	1.7
ASA4: BSC vs chemotherapy HR=2.0	1.74	[redacted]	[redacted]	1.2	2.06	[redacted]	[redacted]	1.7	2.33	[redacted]	[redacted]	1.7
ASA5: SMR=1.57	1.70	[redacted]	[redacted]	1.2	2.01	[redacted]	[redacted]	1.7	2.01	[redacted]	[redacted]	1.7
ASA6: PF utility value = 0.80 and PD utility = 0.68	1.81	[redacted]	[redacted]	1.2	2.13	[redacted]	[redacted]	1.7	2.13	[redacted]	[redacted]	1.7
ASA7: Long-term survivor utility decrement = 0.02	1.77	[redacted]	[redacted]	1.2	2.08	[redacted]	[redacted]	1.7	2.08	[redacted]	[redacted]	1.7
ASA8: Lifileucel administration	1.79	[redacted]	[redacted]	1.2	2.11	[redacted]	[redacted]	1.7	2.11	[redacted]	[redacted]	1.7

Scenario	Lifileucel vs ipilimumab				Lifileucel vs chemotherapy				Lifileucel vs BSC			
	Inc. QALYs	Inc. costs	ICER	DM	Inc. QALYs	Inc. costs	ICER	DM	Inc. QALYs	Inc. costs	ICER	DM
disutility doubled												
ASA9: Non-infused patients receive BSC	1.77	[redacted]	[redacted]	1.2	2.09	[redacted]	[redacted]	1.7	2.09	[redacted]	[redacted]	1.7
ASA10: All chemotherapy patients receive dacarbazine	1.79	[redacted]	[redacted]	1.2	2.11	[redacted]	[redacted]	1.7	2.11	[redacted]	[redacted]	1.7
ASA11: Discount rates = 1.5%	2.27	[redacted]	[redacted]	1.2	2.66	[redacted]	[redacted]	1.7	2.66	[redacted]	[redacted]	1.7
ASA12: Decision modifier = 1.7 for ipilimumab	1.79	[redacted]	[redacted]	1.7	N/a	N/a	N/a	1.7	N/a	N/a	N/a	1.7

AE - adverse event; ASA - additional sensitivity analysis; BSC - best supportive care; DM - decision modifier; EA - exploratory analysis; EAG - External Assessment Group; HR - hazard ratio; HRQoL - Health-related quality of life; ICER - incremental cost-effectiveness ratio; Inc. - incremental.; MCM - mixture-cure model; QALY - quality-adjusted life year; SMR - Standardised mortality ratio. STC - simulated treatment comparison; N/a - not applicable

2. BACKGROUND

This chapter provides a brief summary of the company's description of the disease, the new technology being evaluated (lifileucel) and the company's intended positioning of lifileucel within the existing treatment pathway for patients with unresectable or metastatic melanoma, as described in Sections B.1.2 and B.1.3 of the company's submission (CS).[1] The clinical advisors to the External Assessment Group (EAG) agreed that the company's description of the disease and clinical pathway are accurate.

2.1 Description of the underlying health problem

2.1.1 Disease overview

Melanoma is a type of skin cancer that starts in cells called melanocytes, which are in the deep layer of the epidermis and produce melanin, the pigment that gives skin its colour.[2, 3] Melanoma is the fifth most common cancer in the UK, with approximately 17,500 new cases diagnosed annually in the UK between 2017 and 2019.[4] Almost half of these new cases (49.1%) were in females. Incidence rates in the UK have increased by 147% in the last three decades, and incidence is projected to rise further by 9% between 2023-2025 and 2038-2040, which could lead to 26,500 new cases annually in the UK by 2038-2040.[4]

Risk factors for melanoma include older age (>65 years, although the disease is quite common in younger people compared to other cancer types), sex (male), exposure to ultraviolet (UV) light (around 85% of melanomas are caused by excessive UV light), skin type and colour (white and which burns if in the sun, especially those with fair or red hair and with freckles), number of moles, birthmarks, family history of melanoma, genetic factors and other medical conditions (e.g., chronic immunosuppression), and use of chemicals in the workplace.[1, 5]

Early-stage melanoma can be asymptomatic, with early signs and symptoms often being related to changes in existing moles[1] or the development of a new pigmented or unusual-looking growth on the skin, more often in areas exposed to the sun.[2] Signs in moles that may indicate melanoma transformation may include asymmetrical shape, change in colour, changes in size, unusual border, and change in symptoms (e.g., swollen, new itchiness or bleeding).[2] Symptoms of advanced melanoma skin cancer depend on the location of the cancer in the body, but might include unexplained weight loss, fatigue, pain, hard or swollen lymph nodes, or a hard lump on the skin.[6]

There is no national screening programme for melanoma skin cancer in the UK.[7] Tests and procedures used to diagnose melanoma include physical examination, dermoscopy, taking photographs and removing the lesion for testing (excision biopsy).[2, 8] Staging and risk assessment procedures are determined by disease presentation at diagnosis, and may include a wide local excision, a computed tomography (CT) scan, positron emission tomography (PET), PET/CT, magnetic resonance imaging

(MRI), tests to see if the melanoma has spread to the lymph nodes (which may include sentinel lymph node biopsy, fine needle aspiration or core needle biopsy), blood tests, and genetic testing (including testing for mutations in the BRAF gene).[1, 8]

Treatment options for melanoma skin cancer depend on disease stage. The main treatment for early melanoma is surgery, but may also include an immunotherapy cream. Treatment for later stage disease, where the cancer has spread, might include one or more of the following options: surgery, immunotherapy, radiotherapy, targeted therapy, intralesional therapy (with talimogene laherparepvec [T-VEC]), chemotherapy, combined or not with an electric current (electrochemotherapy), and immunotherapy cream.[9] The specific treatment options and clinical pathway for unresectable or metastatic melanoma are detailed in Section 2.2.

Despite recent advances in the treatment of metastatic disease, the prognosis for unresectable or metastatic melanoma remains poor.[1] Five-year survival rates for patients diagnosed with Stage III disease decline significantly from 69% in Stage IIIC to 32% for Stage IIID (although for many patients the risk of recurrence can be reduced with approved adjuvant systemic therapies), and decline further to 22.5% for patients with Stage IV disease, although a smaller proportion of patients are diagnosed in these stages (16.1% Stage III versus 10.2% Stage IV, respectively).[1] There were approximately 2,300 annual deaths related to melanoma skin cancer in the UK in 2017-2019, making it the 20th most common cause of cancer death in the UK (~1% of all cancer deaths). Almost half of these deaths (48%) were in people aged 75 years and over.[4] Melanoma skin cancer mortality rates have increased by 141% in the UK since the 1970s, but remained stable over the last decade and are projected to fall by 12% between 2023-2025 and 2038-2040.[4]

2.1.2 Disease burden

The CS[1] highlights the burden of all stages of melanoma on patient's health-related quality of life (HRQoL), and states that the disease is ranked eighth amongst all diseases in terms of age-standardised disability-adjusted life year (DALY) rates in the Global Burden of Disease (2021) study. The study estimated that approximately 6.18 million total DALYs were attributed to melanoma globally in 2021, which reflects the impact of the disease on long-term health and HRQoL deterioration associated with the disease.[1] The CS also reports issues experienced by metastatic (Stage III/IV) melanoma patients related to *"sleep problems, primarily due to anxiety, stress, and/or worry related to their condition, pain, or discomfort"* and impacts on emotional wellbeing, with increased depression and fear of recurrence. The CS also highlights the HRQoL burden for caregivers of melanoma patients, with 20-35% of carers experiencing one or more physical health issues whilst providing care to a melanoma patient, and 70% of carers experiencing mental health issues.[1, 10]

The CS[1] mentions the economic burden of melanoma to the healthcare system, with disease management costs increasing as the disease progresses, which are largely driven by increasingly costly new drug therapies which may require long-term treatment, and higher rates of disease- and treatment-related adverse events (AEs). The resource use and costs of managing the high incidence of AEs from immunotherapies, complex surgical resections, palliative care, and administration of chemotherapy are considered to lead to high costs. The high mortality and morbidity associated with the disease, which occur in a high proportion of younger patients (<65 years old), result in a loss of economic productivity and economic burden, with 9,555 years of productivity estimated to be lost due to melanoma in the UK in 2019.[1] The CS also mentions that in Nightingale *et al.*, 25% of caregivers reported high levels of financial burden related to employment absences and out-of-pocket costs.[11]

2.1.3 Description of the technology

Lifileucel (AMTAGVI®) is a tumour-derived autologous T-cell immunotherapy, composed primarily of tumour-derived CD4+ and CD8+ T-cells, manufactured from patient's resected tumour-tissues. The CS[1] describes lifileucel's proposed mechanism of action as follows: *"tumour-derived T-cells enter the tumour microenvironment and mediate tumour cell death through release of cytokines and cytolytic enzymes, promoting cell lysis."* [redacted]

The lifileucel infusion is described by the company as being composed of 1 to 4 patient-specific infusion bag(s) supplied in individual protective metal cassettes. Lifileucel should be administered as a single infusion. The full lifileucel regimen includes procedures through four stages: (i) the tumour tissue resection; (ii) a lymphodepletion (LD) chemotherapy regimen; (iii) the lifileucel infusion and (iv) interleukin 2 (IL-2) therapy. The period between the resection surgery until infusion of lifileucel is expected to take approximately 33 days, whilst the time required for the administration of the overall lifileucel regimen (including LD, lifileucel and IL-2) is estimated to be 11 days.

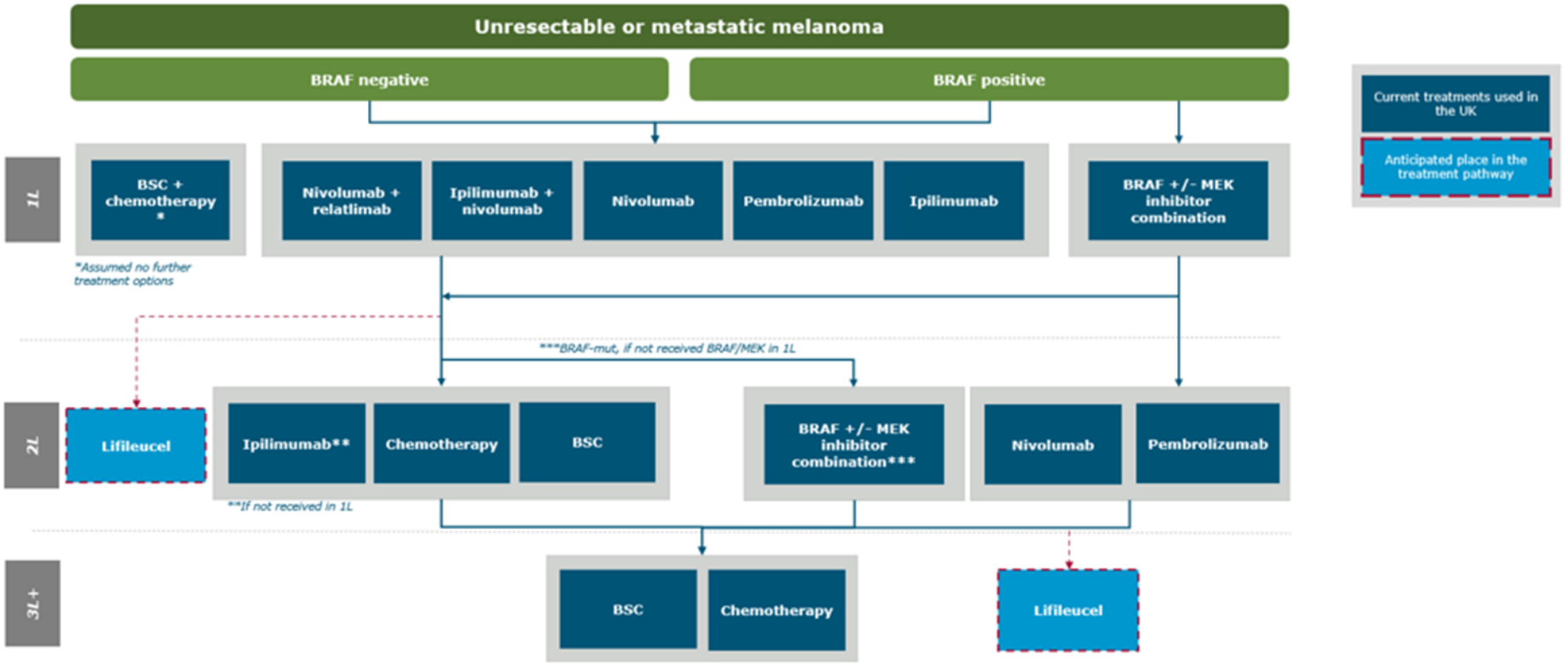
The anticipated marketing authorisation included in the draft SmPC[13] states that lifileucel is indicated [redacted]

2.2 Company's overview of current service provision

2.2.1 Current treatment pathway for unresectable or metastatic melanoma

Section B.1.3.8 of the CS[1] outlines the company's view of the current treatment pathway for adult patients with unresectable or metastatic melanoma. The pathway, together with the proposed positioning of lifileucel, is reproduced in Figure 1.

Figure 1: Company's view of the current treatment pathway and the anticipated positioning of lifileucel (reproduced from CS, Figure 3)



1L - first line; 2L - second line; 3L - third line; BSC - best supportive care; MEK - mitogen-activated protein kinase; NICE - National Institute for Health and Care Excellence
References: CS[1] (page 25), based on the ESMO guideline, NICE Guideline 14 and previous appraisals[14-24]

The CS[1] states that treatment options for patients with unresectable or metastatic melanoma include: immunotherapy via immune checkpoint inhibitors (ICIs) such as pembrolizumab and nivolumab; targeted therapy using signal transduction inhibitors; chemotherapy; and best supportive care (BSC). The main clinical guideline in the UK for the condition is the National Institute for Health and Care Excellence (NICE) Guideline 14 (NG14: Melanoma: assessment and management).[14]

The NICE guideline[14] states that systemic anticancer therapy options for untreated unresectable stage III and stage IV melanoma include immunotherapy as the main first-line (1L) option:

- Nivolumab plus ipilimumab (a PD-1 inhibitor and a cytotoxic T-lymphocyte associated protein 4 [CTLA-4] inhibitor, respectively) as the preferred option; or
- Pembrolizumab or nivolumab monotherapy (both PD-1 inhibitors), if the preferred option is unsuitable or unacceptable.

Where immunotherapy is contraindicated or unsuitable, the guideline recommends alternative treatments based on BRAF type:

- Targeted therapy agents (BRAF kinase inhibitors +/- mitogen-activated protein kinase [MEK] inhibitors) for BRAF V600 mutation-positive patients:
    - Encorafenib plus binimetinib, or dabrafenib plus trametinib if immunotherapies are contraindicated or insufficient time for an adequate immune response is predicted;
    - Dabrafenib or vemurafenib monotherapies if binimetinib and trametinib are contraindicated, or chemotherapy (dacarbazine) or BSC if targeted therapy is contraindicated;
- Chemotherapy (dacarbazine) or BSC for BRAF wild-type patients.

The NICE guideline[14] also states that the choice of the most appropriate treatment should be guided by individual clinical characteristics such as comorbidities and performance status (PS), risk of treatment toxicity and the patient's tolerance to therapy, presence of symptomatic brain metastases, and tumour characteristics (e.g., rapid progression, high disease burden, and lactate dehydrogenase [LDH] levels).[14] The CS[1] notes that relatlimab plus nivolumab has been recommended as a treatment option for 1L therapy by NICE since 2024. The CS also mentions that the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) guidelines[25] also recommend immunotherapy as 1L treatment where clinically possible, with nivolumab plus ipilimumab as the preferred choice, or BRAF and MEK inhibitors for BRAF mutation-positive patients with rapidly progressing disease or contraindications to immunotherapy.

Based on NG14[14] recommendations, the CS[1] refers to options for the next line of therapy for the target population as being largely dependent on previous treatment(s) received. For patients who have not

received previous anti-PD-1 therapy, nivolumab or pembrolizumab monotherapy are recommended as second-line (2L) therapies. If patients have received previous programmed death ligand 1 (PD-L1) inhibitor therapy (and/or BRAF+-MEK inhibitors if BRAF-positive), the options for 2L (or third-line [3L] if BRAF+) would be ipilimumab monotherapy (if not received at 1L), chemotherapy (dacarbazine) or BSC. The CS also mentions that UK clinical experts who attended the company's advisory board meeting in October 2024[26] stated that, given the limited treatment options for these patients, they would refer 20-50% of patients to clinical trials rather than offering ipilimumab, chemotherapy or BSC at 2L or later.[1] The EAG's clinical advisors agreed that a proportion of these patients would be referred for clinical trials due to the lack of alternatives for these patients, since the majority of patients will not be eligible for ipilimumab monotherapy because they will have previously received it in the 1L setting, and because of unsatisfactory outcomes associated with chemotherapy.

Current recommendations for treating unresectable and metastatic melanoma from NICE are summarised in Table 3.

Table 3: Current NICE recommendations for treatments for unresectable or metastatic melanoma

NICE TA	NICE recommendation
TA400	Nivolumab in combination with ipilimumab is recommended, within its marketing authorisation, as an option for treating advanced (unresectable or metastatic) melanoma in adults, only when the company provides ipilimumab with the discount agreed in the patient access scheme.
TA366	Pembrolizumab is recommended as an option for treating advanced (unresectable or metastatic) melanoma that has not been previously treated with ipilimumab, in adults, only when the company provides pembrolizumab in line with the commercial access agreement with NHS England.
TA384	Nivolumab as monotherapy is recommended, within its marketing authorisation, as an option for treating advanced (unresectable or metastatic) melanoma in adults.
TA950	Nivolumab–relatlimab is recommended as an option for untreated advanced (unresectable or metastatic) melanoma in people 12 years and over, only if: • Nivolumab–relatlimab is stopped after 2 years of treatment, or earlier if the cancer progresses, and • The company provides it according to the commercial arrangement.
TA562	Encorafenib with binimetinib is recommended, within its marketing authorisation, as an option for treating unresectable or metastatic BRAF V600 mutation-positive melanoma in adults. It is recommended only if the company provides encorafenib and binimetinib according to the commercial arrangements.
TA396	Trametinib in combination with dabrafenib is recommended, within its marketing authorisation, as an option for treating unresectable or metastatic melanoma in adults with a BRAF V600 mutation only when the company provides trametinib and dabrafenib with the discounts agreed in the patient access schemes.
TA321	Dabrafenib is recommended, within its marketing authorisation, as an option for treating unresectable or metastatic BRAF V600 mutation-positive melanoma only if the company provides dabrafenib with the discount agreed in the patient access scheme.
TA269	Vemurafenib is recommended as an option for treating BRAF V600 mutation-positive unresectable or metastatic melanoma only if the manufacturer provides vemurafenib with the discount agreed in the patient access scheme.

NICE TA	NICE recommendation
TA268	Ipilimumab is recommended as an option for treating advanced (unresectable or metastatic) melanoma in people who have received prior therapy, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme.
TA357	Pembrolizumab is recommended as an option for treating advanced (unresectable or metastatic) melanoma in adults only: • after the disease has progressed with ipilimumab and, for BRAF V600 mutation-positive disease, a BRAF or MEK inhibitor and • when the company provides pembrolizumab in line with the commercial access agreement with NHS England.

TA - Technology Appraisal; NICE - National Institute for Health and Care Excellence; CDF - Cancer Drugs Fund; MAA - Managed Access Agreement

2.2.2 Company's proposed positioning of lifileucel

The company's proposed positioning of lifileucel is in line with its anticipated marketing authorisation (see Section 2.1.3). In response to a request for clarification from the EAG (see clarification response,[27] question A23), the company clarified that the proposed positioning for lifileucel corresponds to second- and subsequent-line therapy for unresectable or metastatic melanoma, depending on patient's BRAF mutation status (i.e., 2L+ for BRAF-wild type and 3L+ for BRAF mutation-positive). The company also stated that the proposed positioning of lifileucel (reproduced in Figure 1) aligns with the anticipated marketing authorisation and the inclusion criteria of Study C-144-01.[28]

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

This chapter presents a summary and critique of the decision problem addressed by the CS.[1] A summary of the decision problem as outlined in the final NICE scope[29] and addressed in the CS is presented in Table 4. The EAG's critique of the decision problem addressed within the CS is presented in the subsequent sections.

Table 4: The decision problem (reproduced from CS, Table 1, with minor amendments by the EAG)

	Final scope issued by NICE[29]	Decision problem addressed in the CS[1]	Rationale if different from the final NICE scope
Population	Adults with previously treated unresectable or metastatic melanoma	[redacted]	Aligned with the draft SmPC[12]
Intervention	• Lifileucel	In line with scope	N/a
Comparator(s)	• Ipilimumab monotherapy • Dacarbazine • Temozolomide • Paclitaxel • Paclitaxel and carboplatin • Best supportive care	Chemotherapy comparators including those listed in the final scope, were grouped into one comparator arm.	Individual product data for chemotherapy in melanoma is not available, therefore, existing pooled data across chemotherapy regimens sourced from the literature was leveraged as a proxy. Clinical expert validation confirmed this approach is appropriate, with no difference in outcomes.
Outcomes	• Progression-free survival • Overall survival • Response rates • Safety • Health-related quality of life	In line with scope	N/a
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to capture the costs and health outcomes of potential long-term survivors and to reflect most of the differences in costs or health	As per final scope issued by NICE: A cost-effectiveness analysis will be performed, expressed in terms of incremental cost per QALYs. A lifetime time horizon of 45 years is used in the base case analysis. Costs will be considered from an NHS and PSS perspective. A simple patient access scheme (PAS) is considered for the intervention. The availability of any commercial arrangements for the	N/a

	Final scope issued by NICE[29]	Decision problem addressed in the CS[1]	Rationale if different from the final NICE scope
	outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be considered.	intervention, comparator and subsequent treatment technologies will be considered. Cost-effectiveness analysis in the proposed population is presented comparing lifileucel with ipilimumab, chemotherapy and best-supportive care. For further details please refer to CS,[1] Section B.3.	

EAG - External Assessment Group; NICE - National Institute for Health and Care Excellence; CS - company's submission; MEK - mitogen-activated protein kinase; SmPC - Summary of Product Characteristics; QALY - quality-adjusted life year; PAS - Patient Access Scheme; PSS - Personal Social Services; N/a - not applicable

3.1 Population

The target population for lifileucel defined in the CS[1] relates to [redacted]. This population is narrower than the population defined in the final NICE scope[29] but is consistent with the anticipated marketing authorisation for lifileucel. The population considered in the CS is also consistent with the study population enrolled in Study C-144-01[28] which is the main source of evidence on the clinical effectiveness of lifileucel.

The EAG's clinical advisors commented that the patients who received the lifileucel infusion in Study C-144-01[28] were broadly representative of those patients who would be considered eligible to receive this treatment in NHS practice.

[redacted]

3.2 Intervention

The intervention described in the CS[1] is consistent with the final NICE scope.[29] The intervention under consideration is lifileucel (AMTAGVI®). Lifileucel does not yet hold a European Medicines Agency (EMA) or Medicines and Healthcare products Regulatory Agency (MHRA) marketing authorisation for the treatment of advanced melanoma. [redacted]

Lifileucel is provided as a single dose for infusion containing a dispersion of tumour-derived T cells.[1] The dose is supplied in one to four patient-specific intravenous (IV) infusion bag(s) in individual protective metal cassettes. Each dose of lifileucel contains [redacted] viable cells.[12] The lifileucel treatment regimen involves the following phases (in order):

- Surgical resection of tumour tissues which will be used in the manufacture of the lifileucel infusion;

- An LD chemotherapy regimen which is given for 7 days before the lifileucel infusion, to remove any negative inhibitory or regulatory cells in the tumour microenvironment (Day -7 to Day-1). The LD chemotherapy includes cyclophosphamide (60mg/kg daily with mesna) via IV infusion for 2 days and fludarabine (25mg/m^2 daily) via IV infusion for 5 days;
- The lifileucel infusion which is infused within 24 to 96 hours after the last dose of chemotherapy;
- Post-lifileucel infusion therapy with IL-2 is administered 3 to 24 hours after the lifileucel infusion is completed to support cell expansion *in vivo* (Day 0 up to Day 4). IL-2 is given at a dose of 600,000 IU/kg every 8 to 12 hours, up to a maximum of 6 doses, and requires a period of monitoring in a hospital setting.

[redacted] The CS[1] indicates a slightly shorter overall turnaround time of around 33 days.

The list price for the lifileucel infusion is [redacted] (excluding other elements of the regimen). The company has a proposed Patient Access Scheme (PAS) discount of [redacted], resulting in a discounted price of [redacted] per patient. The company's economic model assumes that the NHS will only pay for the lifileucel infusion when it is administered and meets the SmPC dose specification. This means that the manufacturer will bear the cost of lifileucel in instances in which a patient is not successfully infused with lifileucel, either due to manufacturer error, discontinuation (e.g., due to disease progression) or death. Based on the assumptions in the company's model, in instances in which patients do not receive the lifileucel infusion or where patients receive an out-of-specification infusion, the NHS is assumed not to bear the costs of the infusion but may incur the costs of other stages of administration (tumour tissue procurement, LD chemotherapy and IL-2 administration).

3.3 Comparators

The NICE scope[29] lists six comparators: (i) ipilimumab monotherapy; (ii) dacarbazine; (iii) temozolomide; (iv) paclitaxel; (v) paclitaxel and carboplatin and (vi) BSC. The CS[1] includes three

comparators: (i) ipilimumab monotherapy; (ii) chemotherapy (represented as a basket of regimens) and (iii) BSC.

The CS[1] presents indirect treatment comparisons (ITCs) of lifileucel versus ipilimumab and lifileucel versus chemotherapy. Patients enrolled in the cohort study used to inform chemotherapy outcomes in the ITC (Mangin *et al.*[30]) received dacarbazine, temozolomide and fotemustine. The chemotherapy arm of the company's economic model uses these data to estimate outcomes for chemotherapy but assumes a different basket of chemotherapy regimens when estimating costs (dacarbazine, temozolomide, carboplatin, carboplatin plus paclitaxel and dacarbazine plus cisplatin). The CS states that using data on a basket of chemotherapy regimens was deemed appropriate by clinical experts, as no difference in outcomes is expected. However, the EAG notes that the minutes of the company's clinical advisory board meeting[26] do not specifically record this view. The EAG's clinical advisors commented that all chemotherapy regimens have limited effectiveness and that they would expect that most patients (around 80-90%) would receive dacarbazine over other chemotherapy regimens.

The CS[1] states that no data are available to quantify outcomes associated with BSC. The minutes of the company's advisory board meeting[26] highlight that some clinical experts considered there to be no difference in outcomes between chemotherapy and BSC. However, a structured elicitation exercise conducted by the company during this meeting resulted in a conclusion that progression and death risks are higher for BSC than chemotherapy. The EAG's clinical advisors stated that outcomes for chemotherapy are likely to be similar to those for BSC.

Whilst not clearly stated in the CS,[1] the company's clarification response[27] (question A3) states that the company considers ipilimumab to be the main comparator for lifileucel. However, the EAG's clinical advisors commented that most patients who are able to receive ipilimumab will have already done so in the 1L setting (in combination with nivolumab). They also stated that chemotherapy is not commonly used in this population due to its unsatisfactory outcomes and toxicity. As such, the EAG believes that BSC is likely to be the main comparator for lifileucel.

3.4 Outcomes

The following outcomes are listed in the final NICE scope:[29]

- Progression-free survival (PFS)
- Overall survival (OS)
- Response rates
- Safety
- Health-related quality of life (HRQoL).

The CS[1] reports on all of these clinical outcomes for patients who received the lifileucel infusion in Study C-144-01.[28] All outcomes data for lifileucel reflect the Pooled Data Aligned with Commercial Specifications (PDAwCS) efficacy set (see Section 4.2.3.1 for details). The company's base case economic model uses data from Study C-144-01 on lifileucel discontinuations, PFS, OS, and AEs. HRQoL data collected in Study C-144-01 were deemed by the company to be unsuitable for use in the economic model; instead, HRQoL estimates were taken from external sources. Further details on the company's model can be found in Section 5.

3.5 Other relevant factors

The CS[1] states that no equality issues have yet been identified for lifileucel.

The EAG notes that the company has made a case that lifileucel is an Advanced Therapy Medicinal Product (ATMP) with curative potential. The CS[1] includes economic analyses which adopt non-reference case discount rates of 1.5% for health outcomes and costs; the EAG's concerns around this issue are discussed in Section 5.3.5.

4. CLINICAL EFFECTIVENESS

The clinical evidence submitted by the company as part of the CS,[1] the CS appendices[13] and the company's clarification response[27] comprise:

- A systematic literature review (SLR),
- A summary and results of a single-arm study of lifileucel (Study C-144-01[28]).
- A summary and results of ITCs comparing lifileucel versus ipilimumab and chemotherapy.

This chapter summarises and critiques the company's review methods and the clinical effectiveness evidence of lifileucel (AMTAGVI®) in previously treated adult patients with unresectable or metastatic melanoma. Full details of the company's SLR are presented in Section 2 of the CS[1] and CS Appendix B.[13]

4.1 Critique of the methods of review(s)

4.1.1 Searches

CS Appendix B[13] presents the search strategy for the clinical effectiveness SLR. The searches were initially carried out in August 2024, and updated in January 2025, with a date limit of post-2014. The EAG considers it best practice to search without a date limit to avoid missing potentially relevant evidence, for example, around the safety of an intervention, and questioned the rationale behind this choice of date cut-off. The company's clarification response[27] (question A10) explains that 2014 marked the introduction of programmed death-1 (PD-1) inhibitors and therefore publications from that point onwards would most reflect the current treatment landscape. While it is the case that ipilimumab was approved for use in 2014, studies related to ipilimumab and other comparator treatments were published before 2014. These studies would have been missed by the company's searches, which the EAG considers to be a cause for some concern.

CS Appendix B.3[13] states that a range of databases were searched, including PubMed-not-MEDLINE, although the company's clarification response indicates that the company incorrectly reported which databases were searched. The company's responses to clarification questions A4 and A5[27] confirm that the databases searched were the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews (CDSR) and Clinical Answers via the Cochrane Library; and Embase via Embase.com. The company's response to clarification response question A4 also states that MEDLINE was not searched separately, but that the MEDLINE supplement available in Embase.com was included instead. The company states that this approach means that a number of publications would not have been retrieved (those indexed in "MEDLINE in-process" or "ahead-of-print") but argues that this would have a *"limited impact on the searches."* The EAG contests this assumption, and instead believes that a more robust approach would have involved searching

MEDLINE-ALL using a dedicated search string designed for that database to avoid the risk of missing potentially relevant up-to-date evidence.

Supplementary search methods included searching trial registers (ClinicalTrials.gov; the European Union [EU] Clinical Trials Register; the World Health Organisation International Clinical Trials Registry Platform [WHO-ICTRP]); relevant conference proceedings from 2022 to January 2025; and the websites of manufacturers of the intervention and comparator products. Additionally, the bibliographies of identified SLRs and network meta-analyses (NMAs) were searched. There was some confusion caused by the reporting of these methods in the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) diagram in Figure 1 of CS Appendix B,[13] as all of these methods were listed under 'Websites' (as explained in response to clarification question A11[27]) and it was unclear from the diagram how many results were retrieved from trial registers, and how many of those results retrieved and screened were included or excluded from the review.

Having framed the review question using the PICOS framework, the company then took the unusual approach of searching for terms related to the Outcome concept, as well as Population, Intervention and Comparators. The EAG questioned the rationale behind this approach, given the recommendations from SuReInfo (Arber *et al.*, 2024[31]) to not include the Outcome element for systematic literature searching. The company's response to clarification question A9(a)[27] sets out the iterative process of search strategy development that the company went through to inform their decision to take this approach, which was largely based on the finding that not including the Outcomes element led to an unmanageable number of irrelevant publications. The EAG recognises that pragmatic decisions sometimes have to be made when designing search strategies and that a balance will need to be struck between sensitivity and specificity. However, sacrificing sensitivity to the extent seen in the CS is the riskier approach in particular when searching for evidence relating to intervention safety and AEs.

CS Appendix B.3.2[13] mentions that filters were used to ensure the search matched the review question, but the company does not report whether published and validated search filters were used. The company's response to clarification question A9(b)[27] confirms that the filters for randomised controlled trials (RCTs) and observational studies used in the Embase.com search (reported in CS Appendix B, Table 2) were based on those from the Scottish Intercollegiate Guidelines Network (SIGN). The EAG considers it best practice to use search filters for relevant study types in their validated form without modification.

For the reasons outlined above, the EAG has concerns around the robustness of the company's search methodology, in particular, the narrow range of databases searched and the lack of a bespoke search of MEDLINE-ALL, and the inclusion of terms for Outcomes, both of which are expected to reduce the

sensitivity of the search and risk missing relevant evidence. In addition, the errors and lack of clarity in some aspects of the reporting in the CS, while corrected or somewhat explained in the company's clarification response, add to the EAG's overall lack of confidence in the literature search for the clinical SLR.

4.1.2 Inclusion criteria

The CS[1] describes an adequate method of identifying and screening references for inclusion in the SLR of clinical effectiveness. Two independent reviewers applied pre-specified inclusion and exclusion criteria (via a two-stage sifting process) to citations identified by the searches. Any disagreements were resolved through discussion or arbitration by a third reviewer (see CS Appendix B.3.3[13] and clarification response,[27] question A12). A summary of the inclusion and exclusion criteria, as reported in CS Appendix B.3.1 is reproduced (with minor changes) in Table 5.

The specified inclusion and exclusion criteria were mostly appropriate and generally reflected the decision problem. While the SLR is comprehensive, its wider remit captures the entire evidence base and informs the company's ITCs. However, as noted in the company's response to clarification questions A13, A14b and A15,[27] it appears that additional inclusion/exclusion criteria were applied to the SLR including those for the ITC. These criteria included: (1) re-running searches and omitting the English-language filter; (2) restricting study selection to studies conducted at sites in Europe while excluding those conducted solely at US centres; (3) including information on prior lines of therapy, and (4) requiring the availability of Kaplan-Meier plots for PFS and OS in included studies. Despite the lack of clarity in the company's responses to clarification questions, including the absence of a convincing supporting clinical rationale for some of the review restrictions, it remains a fundamental prerequisite for a SLR to clearly pre-specify unambiguous inclusion and exclusion criteria as this approach minimises bias and enhances transparency and reproducibility of the review process.[32, 33] The requirement is not fully met in the company's SLR.

Table 5: Inclusion/exclusion criteria used to select studies reporting clinical efficacy and safety in previously treated patients with unresectable or metastatic melanoma in the CS (reproduced with minor changes from CS Appendix B.3.1, Table 1)

Selection criteria	Inclusion criteria	Exclusion criteria
Population	Adult patients with unresectable or metastatic melanoma (stage IIIc, IIId or IV), AND; Previously treated with PD-1 blocking antibody, AND: If BRAF V600 mutation positive, a BRAF +/- MEK inhibitor	Not fulfilling inclusion criteria
Intervention/ Comparators	Lifileucel / AMTAGVI/ LN-144 Ipilimumab Best supportive care (BSC) Chemotherapy (dacarbazine or temozolomide or carboplatin or cisplatin or paclitaxel)	No interventions/ comparators of interest
Outcomes	Efficacy: Overall response rate Duration of response Duration of remission Disease control rate Overall survival (OS) Progression-free survival Safety: Adverse events (AEs) Discontinuation (rates and reasons for)	No reported outcomes of interest
Study type	Randomised clinical trials (including extension studies) Single-arm prospective interventional studies Subgroup analyses of previously published studies Systematic reviews and meta-analyses (for cross-checking only) Pooled analyses (for cross-checking only) Observational studies	Non-human/preclinical studies Individual case study reports
Publication type	Article, conference abstract, conference paper, article in press	Notes** Errata** Comments** Editorials** Review articles***
Language	NA****	NA****
Date	**Original search:** 1 January 2014 – 22 August 2024 **Updated search:** 22 August 2024 – 28 January 2025	**Original search:** Any study from before 1 January 2014 **Updated search:** Any study from before 22 August 2024

***Notes, errata, comments, editorials were checked for corrections of previous published data, only in case of any corrections of relevant data, were these included in the review.*

****Reviews and network meta-analyses were checked for bibliographic references ONLY and were not extracted.*

***** Originally, only English-language studies were included but searches were re-run omitting the English-language filter following a clarification request to question A13*

AE - adverse event; BSC - best supportive care; MEK - mitogen-activated protein kinase; NA - not applicable; OS - overall survival; PD-1 - programmed cell death protein 1; PFS - progression-free survival

4.1.3 Critique of data extraction

The data extracted and presented in the CS[1] for the SLR of clinical effectiveness evidence appear to be appropriate and comprehensive. As noted in the company's clarification response[27] (question A12), all relevant data were extracted by a single reviewer and checked for accuracy by a second independent reviewer. Despite the lack of clarity in the company's clarification response, the EAG assumes that any discrepancies were resolved through discussion. Notwithstanding the issues raised in Section 4.1.1 and 4.1.2, neither the EAG nor its clinical advisors are aware of any additional relevant completed studies of lifileucel within the scope of this appraisal.

4.1.4 Quality assessment

The quality assessment of the included studies in the CS[1] for the SLR and the ITC was undertaken using an appropriate critical appraisal tool. The CS (Appendix B.4.6) used the revised Cochrane Risk of Bias 2 (RoB 2) tool for the assessment of included RCTs[34] and the Downs and Black Checklist for Clinical Trial Quality Assessment for the assessment of non-RCTs.[35] In its clarification response to question A16,[27] the company indicated that the original Downs and Black checklist was used in the CS, with a modification: the scoring for item 27 (Power) was simplified to a binary scale of 0 or 1, rather than the original 0–5 scale. Moreover, as noted in the company's clarification response[27] (question A12), the quality assessment process was performed by a single reviewer and checked by a second reviewer. Despite the lack of clarity in the company's clarification response to question A12, the EAG assumes that any discrepancies were resolved through discussion.

4.1.5 Evidence synthesis

The company conducted a narrative synthesis of the evidence on lifileucel for treating adult patients with unresectable or metastatic melanoma who have previously received treatment. However, the CS[1] (including CS Appendix B.3) does not provide sufficient methodological detail on how this approach was undertaken. Ideally, a narrative synthesis approach should be justified, rigorous (i.e., describe results without being selective or emphasising some findings over others) and transparent to reduce potential bias.[36, 37]

Owing to the lack of head-to-head studies, the company undertook an ITC to evaluate the comparative efficacy of lifileucel with relevant comparators in patients with pretreated, unresectable or metastatic melanoma. Full details (see CS,[1] Section 2.10 and CS Appendix B4.5[13]) and a summary and critique of the methods and results of the ITCs is provided in Sections 4.4 to 4.7.

4.2 Critique of trials of the technology of interest, the company's analysis, and interpretation

4.2.1 Studies included in/excluded from the submission

Alongside discrepancies in the company's PRISMA flow diagram, Figure 1 of the CS[1] does not fully conform to the PRISMA statement (http://www.prisma-statement.org/) as it does not clearly present the complete literature searching and screening process including any updated revisions. Although the EAG requested revised PRISMA diagrams to address missing or unclear details, this information was not clearly provided by the company (see clarification response,[27] question A11). Further details on the key studies involving lifileucel can be found in Section 4.2.3, while information on the studies included in the ITCs is provided in Section 4.4.

4.2.2 Ongoing studies

The CS[1] (Section 2.12) does not cite any ongoing studies that will provide additional evidence for lifileucel in the indication being appraised in the next 12 months.

4.2.3 Main supporting evidence – Study C-144-01

4.2.3.1 Study design

The company's SLR of lifileucel for the treatment of unresectable or metastatic melanoma in previously treated patients identified and included one pivotal study: C-144-01.[28] A summary of this study is provided in Table 6.

Table 6: Summary of Study C-144-01 (adapted from CS, Section 2.2, Table 5; Section B 2.3, Table 6 and Figure 6; and Chesney *et al.*)

Study	C-144-01
Study design	Phase II, open-label, multicohort, multicentre, single-arm study
Location	42 sites across France (2), Germany (8), Hungary (1), Spain (5), Switzerland (1), USA (21) and UK (4)
Population	Adult patients (≥18 years) with unresectable or metastatic melanoma (stage IIIc or stage IV) who progressed following treatment on at least one 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
Intervention(s)	Lifileucel regimen consisting of: *Lifileucel manufacturing*: Melanoma lesions resected (resected tumour diameter ≥1.5 cm) and shipped to a central good manufacturing practice facility for 22-day lifileucel manufacturing to produce tumour-infiltrating lymphocyte cell therapy. *Lifileucel administration*: Lifileucel is administered in a 3-step procedure with approximately an 11-day duration: • Lymphodepletion: pre-treatment with lymphodepleting chemotherapy regimen (cyclophosphamide, 60mg/kg once daily for 2 days followed by fludarabine, 25mg/m^2, once daily for 5 days) in preparation of receiving lifileucel (Day -7 to Day-1). • Lifileucel infusion: Lifileucel is infused approximately 24 hours after the last dose of fludarabine (Day 0) • Beginning 3-24 hours after lifileucel infusion, IL-2 (600,000 IU/kg) is administered every 8-12 hours for up to a maximum of 6 doses (Day 0 up to Day 4). IL-2 infusion requires a period of monitoring in a hospital setting for patients.
Comparator(s)	None (single-arm study)
Primary outcomes	• Objective Response Rate as assessed by an Independent Review Committee per RECIST version 1.1. Time frame: every 6 weeks for 6 months, then every 3 months for a maximum of 60 months
All other reported outcomes specified in the decision problem	• Progression-free survival* • Overall survival* • Response rates • Safety* • Health-related quality of life

** Outcomes used in the company's economic model*
IL-2 - interleukin-2; MEK - mitogen-activated protein kinase; PD-1 - programmed cell death 1; RECIST - Response Evaluation Criteria in Solid Tumors

Study C-144-01 (NCT02360579)[38, 39] is a multinational, Phase II, open-label, single-arm study to assess the efficacy and safety of the lifileucel regimen in adults (≥18 years) with unresectable or metastatic melanoma (Stage IIIC or Stage IV) who had received at least one prior systemic treatment, including a PD-1 inhibitor and, for those with a BRAF V600 mutation, a BRAF inhibitor with or without a MEK inhibitor. Study C-144-01 was conducted in 42 centres across 7 countries (France, Germany, Hungary, Spain, Switzerland, the UK and the USA).

The study was composed of four distinct cohorts. Cohort 1 included patients receiving non-cryopreserved tumour infiltrating lymphocytes (TIL) generated using a manufacturing process which was different to that for lifileucel; patients in Cohort 2 and registrational Cohort 4 received cryopreserved lifileucel. Cohort 3 included patients from Cohorts 1, 2, and 4 who were retreated with lifileucel. Given that non-cryopreserved lifileucel is no longer in clinical use (Cohort 1), and the anticipated marketing authorisation for lifileucel does not include retreatment (Cohort 3), the CS[1] focuses only on patients from Cohorts 2 and 4 (N=153). Although Cohorts 2 and 4 were enrolled during different timeframes, they shared the same eligibility criteria. For further details see the CS,[1] Section 2.3.1, Table 6.

The lifileucel regimen was investigated as a one-time treatment. Figure 2 illustrates the course of the treatment process and post-treatment follow-up. Eligible patients underwent surgical resection of tumour tissues measuring between 1.5 cm and 4.0 cm in aggregate diameter. The excised tumour was then processed (i.e., trimmed and fragmented) and transported to a centralised Good Manufacturing Practice facility (no further details are provided in the CS) for the initiation of lifileucel production. The manufacturing process, which spans 22 days, yielded a cryopreserved TIL infusion product. The treatment protocol was administered in a 3-step procedure and began with the non-myeloablative lymphodepletion (NMA-LD) regimen (cyclophosphamide 60mg/kg with mesna daily for 2 days and fludarabine 25mg/m^2 daily for 5 days), followed by a single infusion of lifileucel and a brief course of high-dose IL-2, which was administered 3 to 24 hours post-lifileucel infusion at a dose of 600,000 IU/kg every 8 to 12 hours, up to a maximum of 6 doses, to promote cell expansion *in vivo*. No bridging therapy was allowed between tumour resection and TIL infusion. The manufacturing procedures and treatment protocols were identical for both Cohorts 2 and 4. Patients who entered the assessment phase were monitored for treatment efficacy until the End-of-Assessment visit (up to five years post-lifileucel infusion), disease progression, or initiation of a new anticancer therapy. Those who completed the End-of-Assessment visit were subsequently followed for OS for up to five years from the time of enrolment or until they withdrew from the study.

Figure 2: Study design: C-144-01 (reproduced from CS, Figure 6)

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.
EOA - End-of-Assessment; ICF - informed consent form; IL-2 - interleukin-2; LD - lymphodepletion; OS - overall survival.

The initial primary endpoint for Cohort 2 was the objective response rate (ORR) as evaluated by investigators. When Cohort 4 was later introduced as a single-arm registrational cohort, its primary endpoint was prospectively defined as ORR assessed by an Independent Review Committee (IRC). To maintain consistency, the primary endpoint for Cohort 2 was subsequently updated to also reflect IRC-assessed ORR. For further details of endpoint definitions see CS,[1] Table 6. Although a pooled analysis of Cohorts 2 and 4 was not originally planned as the primary analysis, it was considered valuable due to the cohorts sharing identical inclusion criteria, the same lifileucel manufacturing process, treatment protocols, and centralised response assessment. An evaluation was also conducted to compare investigator-assessed ORR with IRC-assessed ORR. Secondary endpoints included duration of response (DoR), OS, PFS, and safety, which was assessed based on the incidence, severity, seriousness, relationship to the study treatment, and characteristics of treatment-emergent adverse events (TEAEs) - defined as any AE occurring from the time of lifileucel infusion through to 30 days post-infusion.

The CS[1] presents multiple analysis sets derived from the total screened population, representing a progressively refined cohort of patients who received lifileucel treatment. Table 7 provides a summary of these analysis sets, with participant flow shown in Table 8. In brief, a total of 270 patients were screened across Cohorts 2 and 4. Of these, 189 underwent tumour harvest (TH set), with 111 from Cohort 4 and 78 from Cohort 2. Thirty-three patients did not receive lifileucel, resulting in a Safety Analysis Set (SAS) of 156 patients (89 from Cohort 4, 67 from Cohort 2). The Full Analysis Set (FAS) included 153 patients (87 from Cohort 4, 66 from Cohort 2), excluding those who received an out-of-specification product. A total of [redacted] patients ([redacted] from Cohort 4 and [redacted] from Cohort 2) comprised the Pooled Data Aligned with Commercial Specifications (PDAwCS) analysis set. This set consisted only of patients who had received lifileucel within the proposed SmPC dosing range and which was produced at facilities approved for commercial manufacturing. This group formed the basis for the results presented in the company's economic model. Study C-144-01 was funded by Iovance Biotherapeutics.[38, 39]

Table 7: Analysis sets derived from data in Study C-144-01 (adapted from CS, Table 9)

	Population	Outcomes from the dataset used in analyses
Screened set (N=270)	All patients who had signed ICF and were screened in the study	N/a
TH set (Enrolled set, N=189)	All patients who had tumour resection for the production of lifileucel, regardless of whether they received lifileucel or not	Safety outcomes
SAS (N=156)	All patients who received any lifileucel infusion	Safety outcomes from this analysis set are used in the model
FAS (N=153)	All patients who had received lifileucel that met the manufacturing product specifications as defined by the clinical trial protocol	PFS, OS, response rates and HRQoL
PDAwCS (N=[redacted])	All patients who had received lifileucel that met proposed SmPC dosing range and manufactured at facilities approved for commercial manufacturing	PFS and OS data from this analysis set are used in the cost effectiveness model

FAS - Full Analysis Set; HRQoL - health-related quality of life; ICF - informed consent form; NA - not applicable; OS - overall survival; PDAwCS - pooled data aligned with commercial specifications; PFS - progression-free survival; SAS - Safety Analysis Set; TH - tumour harvested; SmPC - Summary of Product Characteristics; N/a - not applicable

Table 8: Patient disposition in Study C-144-01 for Cohorts 2 and 4 (adapted from CS, Table 10)

	Cohort 4 (N=111)	Cohort 2 (N=78)	Pooled Cohorts 2 and 4 (N=189)
Screened patients	161 (100)	109 (100)	270 (100)
TH Set (Enrolled Set), n (%)	111 (68.9)	78 (71.6)	189 (70)
Patients who did not receive lifileucel	22 (19.8)	11 (14.1)	33 (17.5)
SAS, n (%)	89 (80.2)	67 (85.9)	156 (82.5)
Patients who received lifileucel out-of-specifications	2 (2.2)	0	2 (1.3)
Patients who received lifileucel of $<1x10^9$ viable cells	0	1 (1.5)	1 (0.6)
FAS, n (%)	87 (97.8)	66 (98.5)	153 (98.1)
Patients who received lifileucel of $<7.5x10^9$ or $>72x10^9$ viable cells	[redacted]	[redacted]	[redacted]
Patients who received lifileucel from manufacturing facilities not approved for commercial manufacturing	[redacted]	[redacted]	[redacted]
PDAwCS, n (%)	73 (83.9)	[redacted]	[redacted]

Percentages given as a proportion of the previous analysis set.
FAS - Full Analysis Set; PDAwCS - pooled data aligned with commercial specifications; SAS - Safety Analysis Set; TH - tumour harvested
Source: C-144-01 clinical pack; DCO: 30th June 2023

4.2.3.2 Baseline and disease characteristics

Section 2.3.3 of the CS[1] provides baseline demographic and clinical characteristics data only for the cohort of patients in the PDAwCS analysis set (Table 9 and Table 10 , respectively). For completeness, the company presented the baseline demographics and characteristics of the FAS (N=153) in CS Appendix K.1.[13]

Table 9: Demographic characteristics for the PDAwCS efficacy set (reproduced from CS, Table 7)

Characteristics	Cohort 4 [redacted]	Cohort 2 [redacted]	Pooled Cohorts 2 and 4 [redacted]
Male, n (%)	38 (52.1)	[redacted]	[redacted]
Mean age (SD)	[redacted]	[redacted]	[redacted]
Race, n (%)			
Asian	1 (1.4)	[redacted]	[redacted]
Black or African American	2 (2.7)	[redacted]	[redacted]
White	69 (94.5)	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Mean weight (kg, SD)	[redacted]	[redacted]	[redacted]
Country, n (%)			
United States	[redacted]	[redacted]	[redacted]
France	[redacted]	[redacted]	[redacted]
Germany	[redacted]	[redacted]	[redacted]
Spain	[redacted]	[redacted]	[redacted]
United Kingdom	[redacted]	[redacted]	[redacted]

BMI - body mass index; PDAwCS - pooled data aligned with commercial specifications; SD - standard deviation
Source: C-144-01 clinical pack; DCO: 30th June 2023

Table 10: Baseline disease characteristics for the PDAwCS efficacy set (reproduced from CS, Table 8)

Characteristics	Cohort 4 [redacted]	Cohort 2 [redacted]	Pooled Cohorts 2 and 4 [redacted]
Disease metastasis at Study Entry[a], n (%)			
M0	[redacted]	[redacted]	[redacted]
M1a	[redacted]	[redacted]	[redacted]
M1b	[redacted]	[redacted]	[redacted]
M1c	[redacted]	[redacted]	[redacted]
M1d	[redacted]	[redacted]	[redacted]
Patients with baseline Liver and/or Brain Lesions by IRC, n (%)	[redacted]	[redacted]	[redacted]
Patients with Mucosal Melanoma, n (%)	[redacted]	[redacted]	[redacted]
Stage at study entry, n (%)			
IIIC	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]
Baseline ECOG Score[a], n (%)			
0	41 (56.2)	[redacted]	[redacted]
1	32 (43.8)	[redacted]	[redacted]

Characteristics	Cohort 4 [redacted]	Cohort 2 [redacted]	Pooled Cohorts 2 and 4 [redacted]
≥2	0	[redacted]	[redacted]
Resected tumour site, n (%)			
Lymph Node	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Skin/Subcutaneous	[redacted]	[redacted]	[redacted]
Liver	[redacted]	[redacted]	[redacted]
Lung	[redacted]	[redacted]	[redacted]
Other Visceral	[redacted]	[redacted]	[redacted]
Peritoneal/Retroperitoneal	[redacted]	[redacted]	[redacted]
Breast	[redacted]	[redacted]	[redacted]
Musculoskeletal	[redacted]	[redacted]	[redacted]
% PD-L1 TPS per central laboratory, n (%)			
PD-L1 Positive (TPS ≥1%)	[redacted]	[redacted]	[redacted]
PD-L1 Negative (TPS <1%)	[redacted]	[redacted]	[redacted]
PD-L1 Positive (TPS ≥5%)	[redacted]	[redacted]	[redacted]
PD-L1 Negative (TPS <5%)	[redacted]	[redacted]	[redacted]
BRAF status, n (%)			
Positive	[redacted]	[redacted]	[redacted]
Negative	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Unknown	[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]
Prior therapy category, n (%)			
Anti-CTLA-4	63 (86.3)	[redacted]	[redacted]
Anti-PD-1/PD-L1	73 (100)	[redacted]	[redacted]
Anti-PD-1/CTLA-4 Combo	42 (57.5)	[redacted]	[redacted]
BRAF/MEK Inhibitor[b]	20 (27.4)	[redacted]	[redacted]
IL-2	[redacted]	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]
Mean number of prior therapies (SD)	3.3 (1.69)	[redacted]	[redacted]
Number of Baseline Target and Non-target Lesions Assessed by IRC, n (%)			
≤3	[redacted]	[redacted]	[redacted]
>3	[redacted]	[redacted]	[redacted]

[a] *Baseline value is defined as the last assessment on or before the first dose of LD.*
[b] *Includes patients who have BRAF V600E or V600K mutated melanoma and received a BRAF inhibitor ± a MEK inhibitor.*
CTLA-4 - cytotoxic T-lymphocyte-associated antigen-4; ECOG - Eastern Cooperative Oncology Group; IL-2 - interleukin-2; IRC - Independent Review Committee; LD - Lymphodepletion; LDH - lactate dehydrogenase; max - maximum; MEK - mitogen-activated protein kinase; min - minimum; NA - not available; PD - progressive disease; PD-1 - programmed cell death protein-1; PDAwCS - pooled data aligned with commercial specifications; PD-L1 - programmed death-ligand 1; SD - standard deviation; TPS - tumour proportion score; ULN - upper limit of normal
Source: C-144-01 clinical pack; DCO: 30th June 2023

Among the [redacted] patients in the PDAwCS efficacy set, only [redacted] was enrolled from a UK site. The mean age was [redacted] years, with over [redacted] of patients aged <65 years. Most patients [redacted] had Stage IV melanoma and [redacted] had >3 target and non-target lesions at baseline (IRC-assessed). Patients had received a median of [redacted] prior lines of therapy. [redacted] patients had received prior anti-PD-1/PD-L1 therapy, and [redacted] had also received anti-CTLA-4 therapy. [redacted] (CS,[1] Section 2.3.3). Similar observations were also noted for the FAS population (i.e., all patients who had received lifileucel that met the manufacturing product specifications as defined in the clinical protocol; N=153). Furthermore, as noted in Section 2.3.3 of the CS (and in the publication by Chesney *et al.*[38] for the broader FAS population), some notable differences were observed in the baseline characteristics of patients in the later-enrolled Cohort 4 compared with Cohort 2, which included a higher proportion of patients with Stage IV melanoma, >3 lesions, elevated LDH, and liver and/or brain metastasis. In addition, patients in Cohort 4 received nearly twice the cumulative duration of prior anti-PD-1/PD-L1 therapy. These indicators of higher disease burden and treatment resistance in Cohort 4 are known negative prognostic factors for response and survival in advanced melanoma patients treated with ICIs.[38] As a result, patients in Cohort 4 may be more challenging to treat compared with those in Cohort 2. Despite these differences, the CS (Section 2.3.3) emphasises the similarities between the cohorts in terms of baseline Eastern Co-operative Oncology Group (ECOG) score, BRAF mutation status, and median number of prior therapies. It also noted that both cohorts followed the same eligibility criteria, study assessments, treatment regimens and used lifileucel produced through the same cryopreserved TIL manufacturing process and production formulation.[40] The EAG acknowledges that there are some differences between the two cohorts, but considers that pooling the data is reasonable.

4.2.3.3 Summary and critique of the company's quality assessment

The company's assessment of the design, conduct, and both internal and external validity of Study C-144-01[28] is summarised in Table 11. Whilst the EAG broadly agrees with the company's assessments of methodological quality and risk of bias, as evaluated using the Downs and Black checklist, neither the CS,[1] CS Appendix D.4[13] nor the company's clarification response[27] (question A16) provide an interpretation of the scoring and quality of the study. The EAG notes that in accordance with previous publications[41-44] that have used the Downs and Black checklist, Study C-144-01 would be considered as a poor quality study (scoring ≤14) by the EAG and a fair quality study by the company (scoring

between 15-19). Moreover, no attempt was made in the CS to integrate the assessment of study quality into the findings reported in the CS, or to consider the overall impact of the quality on the results.

Table 11: Quality assessment of Study C-144-01, as assessed by the company (adapted from CS, Table 12 and CS Appendix K.2)

Item	Criteria for measuring study quality	Study C-144-01			
		Company		EAG	
		Assessment	Score*	Assessment	Score*
Reporting					
1	Is the hypothesis/aim/objective of the study clearly described?	Yes	1	Yes	1
2	Are the main outcomes to be measured clearly described in the Introduction of Methods section?	Yes	1	Yes	1
3	Are the characteristics of the patients included in the study clearly described?	Yes	1	Yes	1
4	Are the interventions of interest clearly described?	Yes	1	Yes	1
5	Are the distributions of principal confounders in each group of subjects clearly described?	Yes	2	Yes	2
6	Are the main findings of the study clearly described?	Yes	1	Yes	1
7	Does the study provide estimates of the random variability in the data for the main outcomes?	Yes	1	Yes	1
8	Have all important adverse events that be a consequence of the intervention been reported?	Yes	1	Yes	1
9	Have the characteristics of patients lost to follow-up been described	No	0	No	0
10	Have actual probability values been reported (e.g., 0.035 rather than <0.05)	No	0	No	0
External validity					
11	Were the individuals asked to participate in the study representative of the entire population from which they were recruited?	NR	0	Unable to determine	0
12	Were those individuals who were prepared to participate representative of the entire population from which they were recruited?	Yes	1	Unable to determine	0
13	Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	NR	0	Unable to determine	0
Internal validity – bias					
14	Was an attempt made to blind study subjects to the intervention they have received?	NA	-	NA (single-arm study)	-
15	Was an attempt made to blind those measuring the main outcomes of the intervention?	NA	-	NA (single-arm study)	-
16	If any of the results of the study were based on “data dredging”, was this made clear?	No	0	Unable to determine	0

Item	Criteria for measuring study quality	Study C-144-01			
		Company		EAG	
		Assessment	Score*	Assessment	Score*
17	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and control?	Yes	1	NA (single-arm study)	-
18	Were the statistical tests used to assess the main outcomes appropriate?	Yes	1	Yes	1
19	Was compliance with the intervention(s) reliable?	Yes	1	Yes	1
20	Were the main outcome measures used accurate (valid and reliable)?	Yes	1	Yes	1
Internal validating – confounding (selection bias)					
21	Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	Same population	1	NA (single-arm study)	-
22	Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	Yes	1	NA (single-arm study)	-
23	Were study subjects randomised to intervention groups?	NA**	-	NA (single-arm study)	-
24	Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	NA	-	NA (single-arm study)	-
25	Was there adequate adjustment for confounding in the analyses from which the main findings were found?	NR	0	Unable to determine	0
26	Were losses of patients to follow-up taken into account?	Yes	1	Yes	1
Power					
27	Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	Yes	1	No (Sample size power calculation for cohort 4 only)	0
	Total score	-	18	-	13

** Responses were scored in accordance with the Downs and Black Checklist: Yes = 1, No = 0, and Unable to determine = 0. For Question 5, the standard scoring was applied: Yes = 2, Partially = 1, and No = 0. Overall study quality was assessed by the EAG in line with previously published research15-18 using the following categories: Excellent (26–28), Good (20–25), Fair (15–19), and Poor (≤14). It is important to note that only randomised studies could achieve an Excellent rating according to this scoring system*

*** Discrepancy (error) – reported as Yes in CS, section B.4.6., Table 12*

The EAG considers it important to highlight a key methodological concern with Study C-144-01.[39] Given its single-arm design, it is subject to inherent methodological limitations, including the absence of a control group, limited ability to adjust for confounding variables and an increased risk of bias, all of which may affect the reliability and interpretation of the results.[45-47] In addition, as noted in Section 4.3.2.1, Study C-144-01 was composed of four distinct cohorts. Initially, the study began with a single cohort (Cohort 1) and was later expanded to include three additional cohorts. Cohort 2 was added through a protocol amendment (Version 5, dated February 4, 2017), and Cohort 4 was incorporated in a subsequent amendment (Version 8, dated December 20, 2018). The hypothesis testing procedure, along with the sample size and power calculation, was pre-specified only for Cohort 4.[40, 48]

4.3 Summary and critique of results of Study C-144-01

Based on information reported in Section 2.6 of the CS,[1] this section provides a brief summary of the key results from Study C-144-01[39] over a 4-year follow-up period, as presented in Table 12 (PDAwCS efficacy set) and Table 13 (FAS population). In the PDAwCS efficacy set, the median follow-up for the pooled Cohorts 4 and 2 was [redacted] ([redacted]). In the FAS, the median follow-up was [redacted] for the pooled cohorts (Cohort 4: not reported; Cohort 2: not reported).

4.3.1. Objective response rate (ORR), as assessed by IRC

As of the 30th June 2023 data cut-off (DCO), the pooled results from Cohorts 2 and 4 for the PDAwCS efficacy set demonstrated an ORR of [redacted], as assessed by IRC using Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 criteria, with a complete response rate (CR) of [redacted], a partial response rate of (PR) of [redacted] and [redacted] patients with stable disease (SD). Similar results were observed in the FAS, with an IRC-assessed ORR of [redacted] and 46.4% patients achieving SD, 25.5% achieving PR and 5.9% achieving CR. For further details of best overall response and investigator-assessed results, see CS,[1] Section 2.6.2 (Table 14 for the PDAwCS efficacy set and Table 15 for the FAS) and Section 2.6.3.1. (Table 16 for the investigator-assessed FAS), respectively.

Table 12: Key efficacy outcomes reported in Study C-144-01 for the PDAwCS efficacy set (reproduced from CS, Table 12)

	Cohort 4 only (N=73)	Cohort 2 only ( )	Pooled Cohort 2 and 4
ORR assessed by IRC (%) (95% CI)			
PFS			
Progressive disease and death, n (%)			
PFS assessed by IRC, median months (95% CI)			
OS			
Deaths (%)			
OS assessed by investigator, median months (95% CI)			
DCR			
DCR assessed by IRC, % (95% CI)			

CI - confidence interval; DCR - disease control rate; INV - investigator; IRC - Independent Review Committee; ORR - objective response rate; OS - overall survival; PDAwCS - pooled data aligned with commercial specifications; PFS - progression-free survival
Source: C-144-01 clinical pack; DCO: 30th June 2023

Table 13: Key efficacy outcomes reported in Study C-144-01 for the FAS population (reproduced from CS, Table 13)

	Cohort 4 only (N=87)	Cohort 2 only (N=66)	Pooled Cohort 2 and 4 (N=153)
ORR			
ORR assessed by IRC, % (95% CI)			
ORR assessed by INV, % (95% CI)			
PFS			
Progressive disease and death, n (%)			
PFS assessed by IRC, median months (95% CI)			
OS			
Deaths, n (%)			115 (75.2)
OS assessed by investigator, median months (95% CI)			13.9 (10.6, 17.8)
DOR			
DOR assessed by IRC, median months (95% CI)			
DCR			
DCR assessed by IRC, % (95% CI)			

CI - confidence interval; DCR - disease control rate; DoR - duration of response; FAS - Full Analysis Set; INV - investigator; IRC - Independent Review Committee; ORR - objective response rate; OS - overall survival; PFS – progression-free survival
Source: Medina et al. (2023); C-144-01 clinical pack; DCO: 30th June 2023

4.3.2. Progression-free survival (PFS), as assessed by IRC

The PDAwCS efficacy set had a median follow-up of . In the pooled results from Cohorts 2 and 4, the median PFS, as assessed by the IRC, was

[redacted], with a 1-year PFS rate of [redacted], and a 4-year PFS rate of [redacted]. Similarly, the FAS had a median follow-up of [redacted] with an IRC-assessed median PFS of [redacted], a 1-year PFS rate of [redacted] and a 4-year rate of [redacted]. A summary of the PFS results is presented in Table 12 (PDAwCS efficacy set) and Table 13 (FAS population) and the corresponding Kaplan-Meier estimates are shown in Figure 3 (PDAwCS efficacy set) and Figure 4 (FAS population).

Figure 3: Kaplan-Meier curve of PFS, as assessed by the IRC for the PDAwCS efficacy set (reproduced from CS, Figure 8)

[redacted]

CI - confidence interval; IRC - Independent Review Committee; KM - Kaplan-Meier; PDAwCS - pooled data aligned with commercial specifications; PFS - progression-free survival; TIL - tumour infiltrating lymphocytes
Source: C-144-01 clinical pack; DCO: 30th June 2023

Figure 4: Kaplan-Meier curve of PFS, as assessed by the IRC in the FAS (reproduced from CS, Appendix K.3, Figure 16)

CI - confidence interval; FAS - Full Analysis Set; IRC - Independent Review Committee PFS - progression-free survival; TIL - tumour infiltrating lymphocytes.
Source: C-144-01 clinical pack;[73] DCO: 30th June 2023
*** Data discrepancy: In the figure, median time (95% CI) reported as: ; however, in the CS (Section 2.6.3.2) and Appendix K.3 (Table 55) data are reported as*

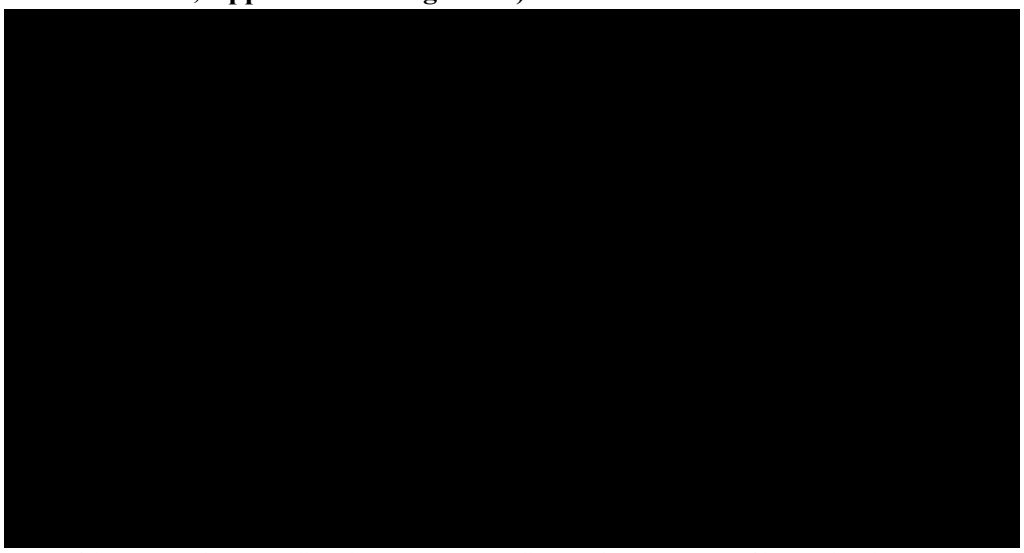
4.3.3. Overall survival (OS), as assessed by investigator

The PDAwCS efficacy set had a median follow-up of . In the pooled results from Cohorts 2 and 4, the median OS, as assessed by the investigators, was , with a 12-month OS rate of . Similarly, the FAS had a median follow-up of months. In the pooled results from Cohorts 2 and 4, the median OS was 13.9 months (95% CI: 10.6, 17.8 months), with a 12-month OS rate of 54.0% (95% CI: 45.6%, 61.6%) . A summary of the OS results is presented in Table 12 (PDAwCS efficacy set) and Table 13 (FAS population) and the corresponding Kaplan-Meier estimates are shown in Figure 5 (PDAwCS efficacy set) and Figure 6 (FAS population).

Figure 5: Kaplan-Meier curve of OS, as assessed by investigator for the PDAwCS efficacy set (reproduced from CS, Figure 9)

CI - confidence interval; KM - Kaplan-Meier; OS - overall survival; PDAwCS - pooled data aligned with commercial specifications; TIL - tumour infiltrating lymphocytes; Source: C-144-01 clinical pack; DCO: 30th June 2023

Figure 6: Kaplan-Meier curve of OS, as assessed by investigator in the FAS (reproduced from CS, Appendix K.3. Figure 17)



CI - confidence interval; FAS - Full Analysis Set; OS - overall survival; TIL - tumour infiltrating lymphocytes' Source: Mediana et al. (2023); DCO: 30th June 2023

4.3.4. Duration of response (DoR), as assessed by IRC

The median DoR of lifileucel in the pooled results from Cohorts 2 and 4 for the FAS population was [redacted] at median study follow-up of [redacted]. The probability of remaining in response was [redacted]% at 12 months, [redacted]% at 24 months, [redacted]% at 36 months, and [redacted]% at 48 months. For further details see CS, Section 2.6.3.4, Table 19. A summary of the DoR results is presented in Table 13 and the corresponding Kaplan-Meier estimates are shown in Figure 7 (FAS population). Results for the PDAwCS efficacy set are not presented in the CS.[1]

Figure 7: Kaplan-Meier curve for DOR, as assessed by the IRC for the FAS (reproduced from CS, Figure 10)

CI - confidence interval; DoR - duration of response; FAS - Full Analysis Set; IRC - Independent Review Committee; KM - Kaplan-Meier; NR - not reached.
Source: C-144-01 clinical pack; DCO: 30th June 2023

4.3.4. Disease control rate (DCR), as assessed by IRC

In the PDAwCS efficacy set, the pooled results from Cohorts 2 and 4 demonstrated a disease control rate (DCR) of , indicating prolonged periods of disease stability or regression. In the FAS for Pooled Cohorts 2 and 4, lifileucel demonstrated a DCR of A summary of the DCR results is presented in Table 12 and Table 13.

4.3.5. Subgroup analysis of ORR (primary endpoint)

A summary of the subgroup analyses is presented in Figure 8. Overall, the ORRs observed across the pre-specified patient subgroups within the FAS (pooled Cohorts 2 and 4) were mostly consistent with those observed in the overall population (31.4%). Importantly, there was little difference between BRAF-negative ( ) and BRAF-positive patients ( ), indicating that lifileucel provides a consistent treatment effect irrespective of BRAF mutation status. However, notable differences were observed in patients with a PD-L1 tumour proportion score (TPS) ≥5% , those with ≤3 baseline target and non-target lesions (or a smaller baseline target lesion sum of diameter (. Despite these differences, the CS appendices[13] state that *"Given the consistency seen across other outcomes, subgroup analyses in the FAS population are assumed to be consistent with the PDAwCS efficacy set."* The EAG notes that the equivalent subgroup analyses for the PDAwCS efficacy set are not presented in the CS.

Figure 8: Forest plot of the ORR by subgroups in the FAS (reproduced from CS, Appendix C, Figure 6)

CI - confidence interval; CTLA-4 - cytotoxic T-lymphocyte-associated antigen-4; ECOG - Eastern Cooperative Oncology Group; IRC - Independent Review Committee; ORR - objective response rate; PD-1 - programmed cell death protein-1; PD-L1 - programmed cell death-ligand-1; TIL - tumour-infiltrating lymphocytes; TPS - tumour proportion score; ULN - upper limit of normal.
Source: C-144-01 clinical pack; DCO: 30th June 2023

4.3.6. Safety and tolerability

This section provides the main safety evidence from Study C-144-01[28] as reported by the company and other published sources, for adult patients with unresectable or metastatic melanoma treated with ≥1 systemic prior therapy including a PD-1-blocking antibody and, if BRAF V600 mutation-positive, a BRAF/MEK inhibitor. The safety data described in this section primarily reflect exposure to lifileucel within a regimen that included cyclophosphamide, fludarabine, and IL-2. The EAG notes that the summary of the safety data presented in the CS[1] reflects AEs for both (1) lifileucel within a regimen that included cyclophosphamide, fludarabine, and IL-2 and (2) lifileucel-only. Given that lifileucel is administered as part of a regimen, the EAG sought clarification on the interpretation of AEs attributed to lifileucel-only (see clarification response,[27] question A22), particularly in light of the US Food and Drug Administration (FDA) clinical review and evaluation of lifileucel,[40] which stated that: *"[the] FDA assessed the contribution of the lifileucel regimen (NMA-LD, lifileucel, and IL-2) as one entity for*

severe and fatal adverse events given that the Applicant has no clinical data to demonstrate the contribution of individual components of the lifileucel regimen to the overall safety." The company's response lacked sufficient details to address this concern and stated only that: *"Lifileucel is only administered as a regimen alongside NMA-LD and IL-2. Section 2.11.3 and Table 27 shows the AE summary for both (1) AEs attributable to the whole treatment regimen, and (2) AEs attributable to lifileucel-only. This provides transparency as to the safety profile for the regimen as a whole, vs the drug only. The cost effectiveness modelling in this submission utilizes data representing the safety profile for the entire regimen."* For further details of AEs see CS, Section 2.11 and Appendix D.[13]

All AEs were recorded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0. The severity of AEs was graded by the study investigators using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

4.3.6.1 Overall exposure

A summary of the extent of exposure in the SAS (i.e., all patients who received any lifileucel infusion) for the lifileucel regimen in Study C-144-01[28] is presented in Table 14. As noted in the US FDA clinical review of lifileucel,[40] in pooled Cohorts 2 and 4 (n=156), patients received a median of 2.0 doses of cyclophosphamide (with a median relative dose intensity [RDI] of 100%) and a median of 5.0 doses of fludarabine (with as median RDI of 99.03%). The median dose of lifileucel was 20.87 x 10^9 viable cells. All but 11 patients (92.9%) received the full planned infusion, with a median relative infusion of 100%. Reasons for not completing the infusion included a damaged infusion bag (n=9) and an anaphylactic reaction to lifileucel (n=2), which led to early termination of the infusion. For the IL-2 administration, all except 3 (98.1%) patients received a median of 6.0 doses (with a median RDI of 100%).

Table 14: Extent of exposure in the SAS (adapted from CS, Appendix D, Table 14 and US FDA clinical review and evaluation of lifileucel)

Regimen	Parameters	Cohort 4 (N=89)	Cohort 2 (N=67)	Pooled Cohorts 2 and 4 (N=156)
LD	**Cyclophosphamide**			
	Number of patients received Cyclophosphamide, n (%)	[redacted]	[redacted]	156 (100)
	Median total number of infusions	[redacted]	[redacted]	2.0
	Median RDI, %[a]	[redacted]	[redacted]	100.00
	Fludarabine			
	Number of patients received fludarabine, n (%)	[redacted]	[redacted]	156 (100)
	Median total number of infusions	[redacted]	[redacted]	5.0
	Median RDI, %[b]	[redacted]	[redacted]	99.03
Lifileucel infusion	Median total infused cells, n x 10^9	[redacted]	[redacted]	20.87
	Median relative infusion	[redacted]	[redacted]	100.00
	Number of patients received full dose of lifileucel, n (%)	[redacted]	[redacted]	145 (92.9)
IL-2	Number of patients received IL-2, n (%)	[redacted]	[redacted]	153 (98.1)
	Median total number of infusions	[redacted]	[redacted]	6.0
	Median RDI, %[c]	[redacted]	[redacted]	100.00

[a] *Relative to 2 planned doses of cyclophosphamide*
[b] *Relative to 5 planned doses of fludarabine*
[c] *Up to maximum of 6 doses of IL-2 at 600,000 IU/kg/dose*
IL-2 - interleukin-2; IU - international units; LD - lymphodepletion; RDI - relative dose intensity; SAS - Safety Analysis Set
Source: C-144-01 clinical pack; DCO: 30th June2023

4.3.6.2 Treatment-emergent adverse events (TEAE)

In Study C-144-01,[28] TEAEs were defined as AEs that occurred from the time of the lifileucel infusion to 30 days post-infusion. In contrast, post-TEAEs were defined as AEs that began 30 days following lifileucel infusion and extended through 6 months post-infusion or until initiation of a new anticancer therapy, whichever occurred first. As summarised in Table 15, all patients in the SAS experienced ≥1 TEAE (any grade) during the course of the study.[38]

Table 15: Adverse event summary for each study period (reproduced from CS, Appendix D, Table 13)

Number of patients with at least one of the following events	Cohort 4				Cohort 2				Pooled Cohort 2 and 4				
	N1	Any Grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)	N1	Any Grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)	N1	Any Grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)	
TH period[a]													
Tumour Harvest AE	[redacted]												
Tumour Harvest SAE	[redacted]												
LD period[b]													
AE during LD period	[redacted]												
SAE during LD period	[redacted]												
SAS[c]													
TEAE	[redacted]												
TEAE related to lifileucel regimen	[redacted]												
TEAE related to lifileucel only[d]	[redacted]												
TEAE leading to lifileucel discontinuation	[redacted]												
Post-Treatment-Emergent AE	[redacted]												
Treatment-Emergent SAE	[redacted]												
Post-Treatment-Emergent SAE	[redacted]												
Treatment-Emergent SAE	[redacted]												

related to lifileucel												
Treatment-Emergent SAE related to lifileucel only[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: AEs are coded based on MedDRA version 24.0. Grades are based on Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Patients with multiple events are counted only once using the maximum grade. Tumour Harvest AEs refer to AEs that started after the tumour harvest and before the start of the LD. For patients who did not receive LD, AEs up to 30 days from tumour harvest are included. AEs during the LD period include AEs that occurred from the start of LD and before the start of the lifileucel infusion. For patients who did not receive a lifileucel infusion, AEs up to 30 days from the last dose of LD are included. TEAEs include AEs that started from the lifileucel infusion to 30 days post lifileucel infusion.
Post-treatment-emergent AEs refer to AEs that started 30 days post lifileucel infusion through 6 months after the lifileucel infusion or up to the start of a new anti-cancer therapy, whichever occurred first.
a Percentage is calculated based on number of patients in TH Set.
b Percentage is calculated based on number of patients who received LD.
c Percentage is calculated based on number of patients in SAS.
d Related to lifileucel only and not related to other components of the treatment regimen (i.e., cyclophosphamide, fludarabine, or IL-2).
AE - adverse event; LD - lymphodepletion; N1 - number of patients in the specific patient population; SAS - Safety Analysis Set; TEAE - treatment-emergent adverse event; TH - tumour harvest
Source: C-144-01 clinical pack; DCO: 30th June 2023

The most common TEAEs in Study C-144-01[28] with an incidence of 20% or higher (any grade) were: [redacted]. The most common Grade 3/4 AEs were: [redacted] (Table 16). The most common post-treatment-emergent AEs with an incidence of ≥5% were: [redacted] (Table 17). As noted in Section 2.11 of the CS[1] and in the US FDA's clinical review of lifileucel,[40] the frequency and severity of most TEAEs were not unusual and were considered predictable and manageable based on the components of the regimen.

Table 16: Most common TEAEs reported at an incidence of ≥ 20% of patients for the SAS (reproduced from CS, Section 2.11.1, Table 26)

System Organ Class Preferred Term	Cohort 4 (N=89)		Cohort 2 (N=67)		Pooled Cohorts 2 and 4 (N=156)	
	Any Grade n (%)	Grade 3/4 n (%)	Any Grade n (%)	Grade 3/4 n (%)	Any Grade n (%)	Grade 3/4 n (%)
Blood and lymphatic system disorders						
Thrombocytopenia[a]						
Anaemia						
Neutropenia[b]						
Febrile neutropenia						
Leukopenia[c]						
Lymphopenia[d]						
Cardiac disorders						
Tachycardia						
Gastrointestinal disorders						
Diarrhoea						
Nausea						
Vomiting						
General disorders and administration site conditions						
Chills						
Pyrexia						
Fatigue						
Oedema peripheral						
Investigations						
Aspartate aminotransferase increased						
Metabolism and nutrition disorders						
Hypophosphatemia						
Hypokalaemia						
Respiratory, thoracic and mediastinal disorders						
Hypoxia						
Skin and subcutaneous tissue disorders						
Rash						

System Organ Class Preferred Term	Cohort 4 (N=89)		Cohort 2 (N=67)		Pooled Cohorts 2 and 4 (N=156)	
	Any Grade n (%)	Grade 3/4 n (%)	Any Grade n (%)	Grade 3/4 n (%)	Any Grade n (%)	Grade 3/4 n (%)
Alopecia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders						
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: AEs are coded based on MedDRA version 24.0. Grades are based on CTCAE version 4.03. Patients with multiple events for a given PT are counted only once using the maximum grade under each PT. AEs are sorted by decreasing frequency of SOC, and of PT within SOC per any grade in the Pooled Cohorts 2 and 4 group. TEAEs include all AEs that began starting from the lifileucel infusion to 30 days post lifileucel infusion.

a AE grouped terms of platelet count decreased and thrombocytopenia

b AE grouped terms of neutrophil count decreased and neutropenia

c AE grouped terms of white blood cell count decreased and leukopenia

d AE grouped terms of lymphocyte count decreased and lymphopenia

AE - adverse event; CTCAE - Common Terminology Criteria for Adverse Events; MedDRA - Medical Dictionary for Regulatory Activities; PT - preferred term; SAS - Safety Analysis Set; SOC - System Organ Class; TEAE - treatment-emergent adverse event.

Source: C-144-01 clinical pack; DCO: 30th June 2023

Table 17: Post-treatment-emergent AEs reported at an incidence of ≥5% for the SAS (reproduced from CS, Section 2.11.1, Table 14)

System Organ Class preferred Term	Cohort 4 (N=89)			Cohort 2 (N=67)			Pooled Cohorts 2 and 4 (N=156)		
	Any grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)	Any grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)	Any grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)
Blood and lymphatic system disorders									
Anaemia	[redacted]								
Thrombocytopenia[a]									
Neutropenia[b]									
Leukopenia[c]									
Lymphopenia[d]									
Gastrointestinal disorders									
Diarrhoea									
Nausea									
Vomiting									
General disorders and administration site conditions									
Fatigue									
Pyrexia									
Infections and infestations									
Sepsis[e]									
Nervous system disorders									
Headache									
Psychiatric disorders									
Insomnia									
Renal and urinary disorders									
Acute kidney injury									
Respiratory, thoracic and mediastinal disorders									
Dyspnoea									
Cough									

a AE grouped terms of platelet count decreased and thrombocytopenia.
c AE grouped terms of white blood cell count decreased and leukopenia.
d AE grouped terms of lymphocyte count decreased and lymphopenia.
e A Grade 5 sepsis was reported in a Cohort 2 patient; the cause of death in this patient was metastatic melanoma complicated by sepsis. Thus, a Grade 5 sepsis event is displayed in AE tables, but this patient was reported as having died of PD in the death section of this CSR.
Notes: AEs are coded based on MedDRA version 24.0. Grades are based on CTCAE version 4.03.
Patients with multiple events for a given PT are counted only once using the maximum grade under each PT.
AEs are sorted by decreasing frequency of SOC, and of PT within SOC per any grade in the Pooled Cohorts 2 and 4 group.
Post treatment-emergent AEs refer to AEs that started 30 days post lifileucel infusion and through 6 months after the lifileucel infusion or up to the start of a new anti-cancer therapy, whichever occurred first.
AE - adverse event; CSR - Clinical Study Report; CTCAE - Common Terminology Criteria for Adverse Events; MedDRA - Medical Dictionary for Regulatory Activities; PD - progressive disease; PT - preferred term; SOC - System Organ Class

Source: C-144-01 clinical pack; DCO: 30th June 2023

4.3.6.3 Deaths

With a median study follow-up of 48.1 months, [redacted] patients died following the lifileucel infusion (Table 18). Of these, six deaths occurred within 30 days after infusion, four of which were attributed to AEs and two to progressive disease.[38] The remaining [redacted] occurred post 30 days following the lifileucel infusion with [redacted] attributed to progressive disease.[86] [redacted] were related to AEs with [redacted] being related to all components of the lifileucel regimen. The cause of the remaining [redacted].

Table 18: Deaths in Study C-144-01 (SAS group) (reproduced from CS, Appendix D, Table 15)

	[redacted]	[redacted]	[redacted]
After lifileucel infusion			
Number of deaths that occur after the lifileucel infusion	[redacted]	[redacted]	[redacted]
After lifileucel infusion to 30 days post lifileucel infusion			
Number of deaths that occur after the lifileucel infusion to 30 days post lifileucel infusion	[redacted]	[redacted]	[redacted]
AE cause of death	[redacted]	[redacted]	[redacted]
PD cause of death	[redacted]	[redacted]	[redacted]
After 30 days post lifileucel infusion			
Number of deaths that occur after 30 days post lifileucel infusion	[redacted]	[redacted]	[redacted]
AE cause of death	[redacted]	[redacted]	[redacted]
PD cause of death	[redacted]	[redacted]	[redacted]
Other cause of death*	[redacted]	[redacted]	[redacted]

**4 were due to an unknown cause, 4 were due to disease progression or metastatic melanoma and 1 described a patient who died in their sleep*
AE - adverse event; PD - progressive disease; SAS - Safety Analysis Set
Source: C-144-01 clinical pack; DCO: 30th June 2023

The EAG notes that, in contrast to the draft SmPC[12] (as provided by the company in the CS, Appendix A[13]) which relates to the anticipated UK licence, the US prescribing information leaflet[49] includes a Boxed Warning for treatment-related mortality, prolonged severe cytopenia, severe infection, internal organ haemorrhage, and cardiopulmonary and renal impairment. The warning emphasises the need for inpatient administration in a hospital setting with intensive care capabilities, and close monitoring of haematologic parameters, organ function, and signs of infection. These measures are intended to help mitigate the potential serious risks associated with the lifileucel regimen.

4.4 Indirect treatment comparison: Selection of studies

Due to the lack of head-to-head randomised studies, the company undertook an ITC to evaluate the comparative efficacy of lifileucel with relevant comparators (ipilimumab, chemotherapy and BSC) in patients with pretreated, unresectable or metastatic melanoma.

4.4.1 General critique of the methods

Notwithstanding the EAG's concerns regarding the date limit applied to the searches (see Section 4.1), the SLR was comprehensive and had a sufficiently broad scope to capture the entire evidence base to inform the company's ITC. A summary of the inclusion and exclusion criteria is reproduced with minor changes in Table 5**.** However, as noted in the company's response to clarification questions A13, A14b and A15,[27] it appears that additional inclusion/exclusion criteria were applied to the ITC SLR (see Section 4.1.2). As the methods used for the ITC SLR, such as literature searching, study selection, data extraction, and quality assessment, were identical to those employed for the lifileucel SLR (see Section 4.1) and therefore share the same limitations.

4.4.2 Studies included in/excluded from the ITC

Alongside discrepancies in the company's PRISMA flow diagram, Figure 1 in the CS[1] does not fully conform to the PRISMA statement (http://www.prisma-statement.org/) as it does not clearly present the complete literature searching and screening process including any updated revisions. Although the EAG requested revised PRISMA diagrams to address these gaps, this information was not clearly provided by the company (see clarification response,[27] question A11).

In brief, following an initial ITC feasibility assessment, the company evaluated eight studies in detail for potential inclusion in a population-adjusted ITC comparing lifileucel with relevant comparators. Of these, five studies reported on ipilimumab,[50-54] two studies on chemotherapy,[30, 55] and one was the pivotal lifileucel study.[30, 38, 55] No studies of BSC were identified. Although not explicitly reported in the CS[1] (Section 2.10.1), the EAG notes that UK clinical experts who attended the company's advisory board meeting[56] identified two potential additional sources of ipilimumab data (VanderWalde *et al*.[57] and Schadendorf *et al*.[58]) for potential inclusion in the ITC. In its response to clarification questions A24 and A25,[27] the company stated that VanderWalde *et al*.[57] was initially considered but was excluded due to its small sample size (N=23), which was deemed insufficient to support a robust unanchored analysis, particularly in the absence of a strong overlap in baseline characteristics with the lifileucel PDAwCS efficacy population. Similarly, the study by Schadendorf *et al.,*[58] was excluded due to the lack of key data on: PD-1 exposure in prior therapy lines, baseline characteristics, and PFS, and exhibited variability in treatment timeframe and dosing. The company considered that these limitations would introduce potential bias and limit the study's suitability for informing ipilimumab effectiveness in the ITC. The EAG broadly agrees with this view. In addition, the remaining studies (N=5)[50, 51, 53-55] were also associated with a number of key issues which precluded their use in an ITC. A summary of the company's assessment, including reasons for study exclusion is provided in Table 19. Overall, only

one ipilimumab study (da Silva *et al.*[52]) and one chemotherapy study (Mangin *et al.*[30]) were considered appropriate by the company for the inclusion in the ITC versus lifileucel.

Table 19: Assessment of studies identified in the SLR for use in the ITC (reproduced with minor amendments from CS, Table 21)

Publication source (author, year)	Trial name/ NCT number	Study type	Population	Rationale for exclusion from ITC
Ipilimumab (N=5)				
Cybulska-Stopa *et al.* (2020)[50]	NR	RWE	Patients with unresectable or metastatic melanoma who had received first-line treatment with nivolumab or pembrolizumab, and second-line treatment with ipilimumab	Patients only received one prior LoT. Inclusion of BRAF V600 mutation positive patients who had not received BRAFi/MEKi.
da Silva *et al.* (2021)[52]	NR	Retrospective cohort study	Patients with unresectable metastatic melanoma who had received previous anti-PD-(L)1 monotherapy (nivolumab, pembrolizumab, or atezolizumab)	N/a – included in ITC
Long *et al.* (2022)[51]	KEYNOTE-006 (NCT01866319)	RCT	Patients with unresectable or metastatic melanoma who had completed or discontinued pembrolizumab after one or more dose and received ipilimumab or BRAFi/MEKi as first subsequent systemic therapy	BRAF V600 mutation positive patients who had not received BRAFi/MEKi were included. Only a few baseline characteristics were reported for the population of interest due to *post hoc* analysis nature. No PFS outcomes were reported.
Rohaan *et al.* (2022)[53]	NCT02278887	RCT	Patients with unresectable metastatic melanoma who had received TIL or ipilimumab following a maximum of one line of prior systemic therapy (excluding ipilimumab)	Patients received zero to one prior LoT. Limited overlap in patient key baseline characteristics (ECOG PS and LDH levels) when compared with the lifileucel population
Wilson *et al.* (2021)[54]	NR	Retrospective RWE study	Patients with metastatic melanoma who had received PD-L1 (nivolumab or pembrolizumab) and ipilimumab, either together or sequentially	Small population size (N=11) in the ipilimumab arm. Limited baseline characteristics reported.
Chemotherapy (N=2)				
Mangin *et al.* (2021)[30]	NR	Retrospective cohort study	Patients with unresectable or metastatic melanoma who had received a first-line treatment by ICI (pembrolizumab,	N/a – included in ITC

Publication source (author, year)	Trial name/ NCT number	Study type	Population	Rationale for exclusion from ITC
			nivolumab, ipilimumab) or BRAF/MEK inhibitors	
Marquez-Rodas *et al.* (2022)[55]	GEM1801	Prospective observational study	Patients with unresectable or metastatic melanoma who had received a second-line treatment with immunotherapy (pembrolizumab, nivolumab, ipilimumab, or other), chemotherapy (including dacarbazine, fotemustine, and others), or targeted therapy (vemurafenib plus cobimetinib, dabrafenib plus trametinib, encorafenib plus binimetinib)	Small population size (N=29). Limited baseline characteristics reported PFS and OS KM curves were reported by BRAF mutation status only, and were not available for the full study population.

BRAFi - BRAF inhibitor; CTLA4 - cytotoxic T-lymphocyte-associated protein 4; ECOG PS - Eastern Cooperative Oncology Group Performance Status; ICI - immune checkpoint inhibitor; ITC - indirect treatment comparison; LDH - lactate dehydrogenase; LoT - line of treatment; MEKi - mitogen-activated protein kinase inhibitor; N/a - not applicable; NR - not reported; PD-(L)1 - programmed death (ligand) 1; RCT - randomised controlled trial; RWE - real-world evidence; SLR - systematic literature review; TIL - tumour infiltrating lymphocytes

4.4.3 Studies included in the ITC

A summary of the studies included in the ITC is presented in Table 20. In general, all included studies recruited patients with unresectable (stage III or IV) or metastatic melanoma who had received PD-1 inhibitors before initiating the treatment with lifileucel, ipilimumab or chemotherapy. Further details of these studies are provided in the following subsections.

Table 20: Summary of studies included in the ITC (adapted from CS, Table 8)

Study identifier	Study design	Population	Intervention and comparators	Location	Prior PD-1 treatment?	KM plots reported in target population	
						PFS	OS
Lifileucel (n=1)							
C-144-01[28, 38]	Open-label prospective study	Patients with unresectable or metastatic melanoma who progressed following treatment on at least one 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	Lifileucel regimen (pre-treatment with LD, a single infusion of lifileucel, post-infusion administration of IL-2)	42 centres in Europe and US	Yes	Yes	Yes
Ipilimumab (n=1)							
da Silva *et al.* (2021)[52]	Real-world retrospective cohort study	Patients with metastatic melanoma (unresectable stage III and IV), resistant to anti-PD-L1 (nivolumab, pembrolizumab, or atezolizumab)	Ipilimumab monotherapy or ipilimumab plus anti-PD-1 (nivolumab or pembrolizumab)	15 melanoma centres in Australia, Europe, and US	Yes	Yes	Yes
Chemotherapy (n=1)							
Mangin *et al.* (2021)[30]	Real-world retrospective cohort study	Patients with an unresectable stage III or IV metastatic melanoma who received a first-line treatment with ICI (pembrolizumab, nivolumab, ipilimumab) or MAPKi (BRAF/MEK inhibitors)	Cytotoxic chemotherapy: dacarbazine, temozolomide and fotemustine	A single centre in France	Yes	Yes	Yes

DTIC - dacarbazine; ICI - immune checkpoint inhibitor; MEK - mitogen-activated protein kinase; LD - lymphodepletion; NR - not reported; OS - overall survival; PD-1 - programmed death (ligand) 1; PFS - progression-free survival; US - United States

4.4.3.1 Lifileucel

The lifileucel study (C-144-01) is described in Section 4.2.3 of this report.

4.4.3.2 Ipilimumab

The ipilimumab study reported by da Silva *et al.*[52] was identified by the company as being the most appropriate source of ipilimumab data to inform the ITC versus lifileucel due to its alignment in study design with Study C-144-01 and the similarity in baseline characteristics (see Table 21). This retrospective, multicentre cohort study was conducted across 15 centres in Australia, Europe, and the USA. It included adult patients (≥18 years) with unresectable stage III or IV metastatic melanoma who were resistant to anti-PD-(L)1 therapy. Patients received either ipilimumab monotherapy (n=162) or ipilimumab plus anti-PD-1 therapy (nivolumab or pembrolizumab; n=193), with treatment decisions based on clinical judgement and therapy availability. Tumour response and clinical outcomes were assessed using routine imaging (CT or PET/CT) every 3 months. The study's primary endpoints included ORR, PFS, and OS. Safety outcomes, including the incidence of Grade 3–5 AEs, were also assessed to determine the tolerability of each treatment regimen. As noted by the company (CS,[1] Section 2.10.1), baseline characteristics were reported for all but one key prognostic factor and treatment effect modifier (target lesion sum of diameters) and were broadly consistent with the inclusion and exclusion criteria for Study C-144-01.[28] The methods for assessing PFS and OS, as well as the reported outcomes, were generally consistent with Study C-144-01. However, Section 2.10.1 of the CS acknowledges that it was unclear whether PFS was assessed by IRC in da Silva *et al.*[52]

The EAG notes whilst the company selected da Silva *et al.*[52] on the basis of having similar baseline characteristics to Study C-144-01,[28] the CS[1] also states that the company elected to undertake a simulated treatment comparison (STC) due to *"the absence of strong overlap in baseline characteristics"*[1] between Study C-144-01 and da Silva *et al.*

4.4.3.3 Chemotherapy

The study by Mangin *et al.*[30] was identified by the company as the only relevant source of evidence for the chemotherapy comparator, as it included regimens (dacarbazine and temozolomide) that reflected the comparator treatments in the NICE scope[29] and had similar inclusion criteria to those for Study C-144-01.[28] This was a retrospective cohort study involving 88 patients with metastatic melanoma who received cytotoxic chemotherapy following prior treatment with either ICIs (n=50) or mitogen-activated protein kinase (MAPK) inhibitors (n=38). The study evaluated PFS, OS, ORR, and DCR. As highlighted by the company (CS,[1] Section 2.10.1), the study had a small sample size, particularly for the chemotherapy cohort, which included only 50 patients who received either dacarbazine (n=28), temozolomide (n=21), or fotemustine (n=1) following prior ICI treatment. The company highlighted that population-adjusted ITCs typically require a larger sample size to reduce uncertainty in treatment

effects. Due to the small sample size, any comparison would rely on limited data, which introduces uncertainty into the analysis. As a result, the company deemed Mangin *et al.*[30] unsuitable for inclusion in a population-adjusted indirect comparison with lifileucel; instead, a naïve, unadjusted ITC was conducted for lifileucel versus chemotherapy.

The EAG notes that there is limited overlap in several covariates between Study C-144[28] and Mangin *et al.*[30] (in particular ECOG PS, see Section 4.4.3). Applying population adjustment using an STC would not fully address this overlap issue; however, undertaking a naïve comparison will fail to account for the chemotherapy patients being less fit than the lifileucel population.

Table 21: Baseline characteristics of studies identified for ITC (adapted from CS Appendix B, Table 9)

Baseline characteristics	Lifileucel	Ipilimumab	Chemotherapy
	C-144-01[28] (N=153)	da Silva *et al.*[52] (N=162)	Mangin *et al.*[30] (N=50)
Gender, n (%)*	Male: 83 (54.2) Female: 70 (45.8)	Male: 103 (64) Female: 59 (36)	Male: 26 (52.0) Female: 24 (48.0)
Median age (range)*	56.0 (20-79)	67 (58-74)	68.25 (NR, SD: 13.27)
Disease stage, n (%)	IIIC: 10 (6.5) IV: 143 (93.5)	III/M1a/M1b: 44 (27) M1c/M1d: 118 (73)	IIIcd-IVM1ab: 7 (14.0) IVM1c: 23 (46.0) IVM1d: 20 (40.0)
Disease metastasis stage, n (%)*	M0: 0 M1a: 9 (10.3) M1b: 12 (13.8) M1c: 54 (63.2) M1d: 11 (12.6)		
Liver metastases, n (%)	By IRC: 59 (38.6) By IA: 55 (35.9)	55 (34)	NR
Brain metastases, n (%)	NR	43 (27)	32 (64.0)
Target lesion sum of diameter by IRC, n (%)*	<70 mm: 49 (32.0) ≥70 mm: 100 (65.4)	NR	NR
ECOG score, n (%)*	0: 84 (54.9) 1: 68 (44.4) ≥2: 1 (0.7)	0: 64 (40) ≥1: 95 (60)	0–1: 16 (39.0) 2-3-4: 25 (61.0)
BRAF mutation status, n (%)	Mutated: 41 (26.8) Wild-type: 103 (67.3) Other: 6 (3.9) Unknown: 3 (2.0)	Mutated: 34 (21) Other: 26 (16) Wild-type: 102 (63)	Mutated: 0 (0.0) Wild-type: 34 (68.0) Other: 14 (28.0) Unknown: 2 (4.0)
LDH level, n (%)*	≤ULN: 70 (45.8) 1-2 x ULN: 54 (35.3) >2 x ULN: 29 (19.0)	Normal: 95 (63) >ULN: 57 (38) Missing values: 10	>Normal: 32/42 (76.2%)
Line of therapy	Median: 3.0 (range: 1, 9)	NR	NR
Median time from last prior anti-PD-1	4.57 months (1.15-56.54)	3.0 months (1.0, 24.4)	NR
Mucosal melanoma, n (%)	12 (7.8)	13 (8)	6 (12.0)

**Key prognostic factor / treatment effect modifier, as identified by UK clinical experts[56]*
AJCC - American Joint Committee on Cancer; CSR – Clinical Study Report; ECOG - Eastern Cooperative Oncology Group; FAS - Full Analysis Set; IA - investigator assessment; IRC - Independent Review Committee; ITC - indirect treatment comparison; LDH - lactate dehydrogenase; NR - not reported; PD-1 - programmed death (ligand) 1; TNM - tumour, node, metastases; ULN - upper limit of normal

4.4.4 Summary of the company's quality assessment

The company's assessment of the design, conduct, and internal and external validity of the ipilimumab and chemotherapy studies is summarised in Table 22. The company's quality assessment of Study C-144-01 was presented previously in Section 3.2.3.3. Due to time constraints of the appraisal process, the EAG was unable to fully assess the quality of the ipilimumab and chemotherapy studies using the Downs and Black checklist. Additionally, the company did not provide an interpretation of the scores or the overall study quality. The EAG notes that in accordance with previous publications[41-44] that have used the Downs and Black checklist, both studies (da Silva *et al.*[52] and Mangin *et al.*[30]) would be classified as being of fair quality, with scores ranging from 15 to 19.

Table 22: Quality assessment of the ipilimumab and chemotherapy studies, as assessed by the company (adapted from CS, Table 12 and clarification response, question A16) using the Downs and Black checklist

Item	Criteria for measuring study quality	Ipilimumab		Chemotherapy	
		da Silva *et al.*[52]		Mangin *et al.*[30]	
		Assessment	Score*	Assessment	Score*
Reporting					
1	Is the hypothesis/aim/objective of the study clearly described?	Yes	1	Yes	1
2	Are the main outcomes to be measured clearly described in the Introduction of Methods section?	Yes	1	Yes	1
3	Are the characteristics of the patients included in the study clearly described?	Yes	1	Yes	1
4	Are the interventions of interest clearly described?	Yes	1	Yes	1
5	Are the distributions of principal confounders in each group of subjects clearly described?	Yes	2**	No	0
6	Are the main findings of the study clearly described?	Yes	1	Yes	1
7	Does the study provide estimates of the random variability in the data for the main outcomes?	Yes	1	Yes	1
8	Have all important adverse events that be a consequence of the intervention been reported?	Yes	1	Yes	1
9	Have the characteristics of patients lost to follow-up been described	No	0	No	0
10	Have actual probability values been reported (e.g., 0.035 rather than <0.05)	Yes	1	Yes	1
External validity					
11	Were the individuals asked to participate in the study representative of the entire population from which they were recruited?	Unable to determine	0	Unable to determine	0
12	Were those individuals who were prepared to participate representative of the entire population from which they were recruited?	Yes	1	Yes	1
13	Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	Unable to determine	0	Unable to determine	0
Internal validity – bias					
14	Was an attempt made to blind study subjects to the intervention they have received?	N/a	-	N/a	-
15	Was an attempt made to blind those measuring the main outcomes of the intervention?	N/a	-	N/a	-

16	If any of the results of the study were based on "data dredging", was this made clear?	No	0	No	0
17	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and control?	Yes	1	Yes	1
18	Were the statistical tests used to assess the main outcomes appropriate?	Yes	1	Yes	1
19	Was compliance with the intervention(s) reliable?	Yes	1	Yes	1
20	Were the main outcome measures used accurate (valid and reliable)?	Yes	1	Yes	1
Internal validating – confounding (selection bias)					
21	Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	Different intervention groups	1	Different intervention groups	1
22	Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	Yes	1	Yes	1
23	Were study subjects randomised to intervention groups?	No	0	No	0
24	Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	N/a	-	N/a	-
25	Was there adequate adjustment for confounding in the analyses from which the main findings were found?	N/a	-	N/a	-
26	Were losses of patients to follow-up taken into account?	No	0	Yes	1
Power					
27	Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	Yes	1	Yes	1
	Total score	-	18†	-	17

** Not reported in the CS or in the company's response to clarification question A16. Therefore, the EAG assumes that responses were scored in accordance with the Downs and Black Checklist: Yes = 1, No = 0, and Unable to determine = 0. For question 5, the standard scoring was applied: Yes = 2, Partially = 1, and No = 0. Overall study quality was assessed by the EAG in line with previously published research[41-44] using the following categories: Excellent (26–28), Good (20–25), Fair (15–19), and Poor (≤14). It should be noted that only randomised studies could achieve an Excellent rating according to this scoring system*

*** Potential scoring discrepancy - for question 5, the standard scoring is: Yes = 2, Partially = 1, and No = 0*

† The company's response to clarification question A16 reports score as 16; however, the source of discrepancy remains unclear to the EAG

4.5 Indirect treatment comparison: Summary of statistical methods and results

4.5.1 Overview of ITC analyses

Owing to the single-arm nature of the Study C-144-01,[28] the company adopted an unanchored ITC approach to estimate the relative treatment effect of lifileucel versus ipilimumab and lifileucel versus chemotherapy. For the comparison of lifileucel and ipilimumab, the company adjusted for population differences using an STC approach for both PFS and OS outcomes, with da Silva *et al.*[52] informing outcomes for ipilimumab. For the comparison of lifileucel and chemotherapy, an unadjusted (naïve) ITC analysis was presented, with Mangin *et al.*[30] informing outcomes for chemotherapy. Owing to the lack of available data, outcomes for BSC were modelled based on assumptions (see Section 5.2).

4.5.2 ITC for lifileucel versus ipilimumab (STC-adjusted)

For the ITC analyses of lifileucel and ipilimumab, pooled individual patient data (IPD) ([redacted]) from both Cohort 2 and Cohort 4 of Study C-144-01[28] were used for lifileucel; pseudo-IPD reconstructed from digitised survival curves published in da Silva *et al.*[52] were used for ipilimumab. An unanchored STC approach was adopted to adjust for the population imbalance between Study C-144-01 and da Silva. STC is an outcome regression approach, whereby a statistical model was fitted using the IPD from Study C-144-01 with appropriate covariates, and then the fitted model was used to predict the outcomes that would have been observed in the da Silva population.

Summary of the methods for the STC

The CS[1] states that an STC approach was preferred over a matching-adjusted indirect comparison (MAIC) approach as there is published evidence to suggest that an STC may provide more accurate estimates than a MAIC where there is poor overlap in baseline characteristics across datasets.[59] Four key assumptions for conducting an unanchored ITC were stated in the CS: (1) homogeneity of outcomes in each treatment; (2) stable unit treatment value; (3) conditional constancy of absolute effects and (4) correct model specifications.

The STC analysis included three key steps. The first step was to fit a Cox regression model to the IPD in Study C-144-01[28] with selected effect modifiers and prognostic variables. The second step was to predict the survival probabilities after simulating patient-level covariates based on the reported patient characteristics in the da Silva study.[52] Adjusted Kaplan-Meier curves and pseudo-IPD for the comparator da Silva population receiving lifileucel were then obtained from the predicted survival probabilities. The third step was to calculate the hazard ratio (HR) 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.

As part of the company's clarification response[27] (question A27), the company provided R code for the STC. The survival probabilities were predicted at the patient-level for a synthetic population with characteristics matching the comparator population using time points from the IPD Kaplan-Meier estimates up to the last event that occurred. The medians of the patient-level survival probabilities were then used to represent the expected outcomes if the da Silva population were given lifileucel, and to inform the adjusted Kaplan-Meier curves and the reconstruction of the IPD.

Covariates

The CS[1] states that prognostic variables and effect modifiers identified after discussions with UK clinical experts included age, sex, ECOG PS score, LDH levels, target lesion sum diameter and line of therapy. The EAG could not find detailed information regarding discussions with UK clinical experts on the selection of prognostic variables and effect modifiers from the minutes of the company's clinical advisory board meeting.[26, 56] A summary of the baseline patient and disease characteristics from the Study C-144-01[28] and the da Silva study[52] are presented in Table 23.

Table 23: Summary of baseline patient and disease characteristics in studies considered for the STC analysis (adapted from CS, Table 22)

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]	-		
ECOG score, n (%):				

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?
0	[redacted]	64 (39.5)	**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)
1		88 (54.3)		
≥2		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		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		102 (63)		
Other	[redacted]	26 (16)		
Unknown		0		
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		43 (26.5)		
Time from last prior anti-PD-(L)1, median (range)	[redacted]	3.0 months (1.0-24.4)		

ECOG - Eastern Cooperative Oncology Group; LDH - lactate dehydrogenase; NR - not reported; PD-(L)1 - programmed death (ligand) 1; SD - standard deviation; ULN - upper limit of normal.

In response to clarification question A28,[27] the company argued that patients in Study C-144-01[28] appeared to be less fit than patients in da Silva *et al.*[52] On average, Study C-144-01 patients were younger and less frail based on median age ([redacted] years vs 67.0 years) and the proportion of patients with an ECOG PS of 0 ([redacted] vs 39.5%). The comparison of patient fitness is unclear with respect to disease stage due to missing metastases information for staging classification for 24 patients in Study C-144-01. The proportion of Stage IIIC/IV M1a/IV M1b patients is 27% in da Silva and the proportion

of Stage IIIC/IV M1a/IV M1b in Study C-144-01 is between 26% and 49%, depending on the disease stage of the [redacted] unknown patients. If at least one of the [redacted] unknown Stage IV patients were at Stage IV M1a/M1b, this would mean that the C-144-01 population is fitter as it has a higher proportion of patients at early disease stage. Study C-144-01 has a lower proportion of patients with normal LDH levels ([redacted] vs 62.5%) and a slightly higher proportion of patients with mutated BRAF status ([redacted] vs 21%). Insufficient information has been collected on melanoma subtype and location of metastases to make a comparison of patient fitness with respect to these characteristics.

The EAG notes that some additional assumptions were made in order to simulate patient-level covariates matching the da Silva population. The company assumed there are 70 patients at the age of 58 years, 70 patients at the age of 74 years and 22 patients at the age of 67 years, as only the median and range were reported for age in da Silva. The EAG notes that the company's assumed age distribution is unlikely to reflect the data in da Silva and notes that the likely impact of adjusting for this covariate is unclear. Due to differences in the categorisation of disease stage, the company's code assumed that 27% of patients are at stage IIIC and 73% of patients are at stage IV, whereas in the da Silva publication, 27% of patients were reported to be at stage III/M1a/M1d, and 73% of patients were reported to be at stage M1c/M1d. The EAG notes that this may have made the simulated population slightly healthier than the da Silva population. For ECOG PS, the company has assumed that 41% of patients have an ECOG PS of 0 and 59% of patients have an ECOG PS of 1, whereas in the da Silva publication, 39.5% of patients were reported to have an ECOG PS of 0, 54.3% of patients were reported to have an ECOG PS of 1, and 4.3% of patients were reported to have an ECOG PS higher than 1. The EAG notes that this may have also made the simulated population slightly healthier than the da Silva population. Also, the company assumed that the covariates are independent of each other when simulating patient-level covariates. The likely impact of this is unclear.

Results of the company's STC

The covariates considered in the company's base case STC analysis include age, sex, disease stage, ECOG PS and LDH levels. Target lesion sum diameter and line of therapy were not considered in the analysis as they were not collected in da Silva.[52] The adjusted HRs for lifileucel versus ipilimumab were estimated to be [redacted] The unadjusted HRs were estimated to be [redacted].

In response to clarification question A27,[27] the company presented the full model output of the Cox regression model including the estimated coefficients. The model output suggests that LDH levels have the greatest effect on the results, followed by disease stage, ECOG score, and BRAF status, while the

impact of age and sex is minimal. The 95% CIs for LDH levels do not include the null effect, indicating that patients with high LDH levels have significantly worse outcomes compared to patients with normal LDH for both PFS and OS. The exponentiated coefficients for disease stage and ECOG PS were estimated to be greater than 1.0, suggesting that patients with disease stage IV and an ECOG score of 1 have worse outcomes compared to patients at stage IIIC and those with an ECOG score of 0, respectively. The exponentiated coefficients for BRAF status were also estimated to be greater than 1.0 but the EAG is unable to determine which group has a worse outcome as the reference category used for BRAF status is unknown. The exponentiated coefficient for sex is smaller than 1.0 for PFS but greater than 1.0 for OS, and the exponentiated coefficient for age is close to 1.0 for both PFS and OS, suggesting a small impact of adjusting for these covariates on the results.

Further results from the company's sensitivity analyses and scenario analyses are presented in Table 26 to show the impact of adjusting for different sets of covariates. The adjusted HRs excluding LDH levels are [redacted], which are quite close to the unadjusted HRs, meaning that the differences between the adjusted and the unadjusted HRs are largely caused by adjusting for the LDH levels. The differences in adjusted HRs between the base case STC analysis and the leave-one-out sensitivity analyses are considerably smaller when age, sex, ECOG score, and disease stage are excluded, compared to when LDH level is excluded. The differences in adjusted HRs between the base case STC analysis and the scenario analysis are also small when BRAF status is included.

The adjusted and unadjusted Kaplan-Meier curves of lifileucel versus ipilimumab for PFS and OS are presented in Figure 9 and Figure 10, respectively. The adjusted curve is higher than the unadjusted curve for both PFS and OS, indicating that the da Silva population would have had better outcomes than the Study C-144-01 population when given lifileucel. In addition, after inspection of the log-cumulative hazard plots, Schoenfeld residual plots, quantile-quantile (QQ) plots and smoothed hazard rate plots for both PFS and OS, the company concludes that there is evidence suggesting a violation of the proportional hazards (PH) assumption and the accelerated failure time (AFT) assumption and that independent model fitting may be more appropriate for survival extrapolation.

Table 24: Full model output of the fitted Cox regression models for the base case STC (reproduced from company's clarification response, Table 1)

Covariate	PFS		OS	
	Exponential (coefficients)	95% CI	Exponential (coefficients)	95% CI
Age	[redacted]	[redacted]	[redacted]	[redacted]
Sex	[redacted]	[redacted]	[redacted]	[redacted]
Disease stage	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS	[redacted]	[redacted]	[redacted]	[redacted]

LDH levels		[redacted]			[redacted]			[redacted]			[redacted]	

CI - confidence interval; ECOG PS - Eastern Cooperative Oncology Group Performance Status; LDH - lactate dehydrogenase; OS - overall survival; PFS - progression-free survival; STC - simulated treatment comparison

Table 25: Full model output of the fitted Cox regression models for the STC scenario analysis with BRAF status included (reproduced from company's clarification response, Table 3)

Covariate	PFS		OS	
	Exponential (coefficients)	95% CI	Exponential (coefficients)	95% CI
Age	[redacted]	[redacted]	[redacted]	[redacted]
Sex	[redacted]	[redacted]	[redacted]	[redacted]
Disease stage	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS	[redacted]	[redacted]	[redacted]	[redacted]
LDH levels	[redacted]	[redacted]	[redacted]	[redacted]
BRAF status	[redacted]	[redacted]	[redacted]	[redacted]

CI - confidence interval; ECOG PS - Eastern Cooperative Oncology Group Performance Status; LDH - lactate dehydrogenase; OS - overall survival; PFS - progression-free survival; STC - simulated treatment comparison

Table 26: Summary of leave-one out STC results for lifileucel versus ipilimumab (adapted from Table 61 in CS, Appendix L and company's clarification response, Table 2)

	PFS		OS	
	HR (95%)	*p*-value	HR (95%)	*p*-value
Base case analysis				
Unadjusted	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted (all covariates included)	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analyses (leave-one-out approach from base-case analysis)				
Age excluded	[redacted]	[redacted]	[redacted]	[redacted]
Sex excluded	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS excluded	[redacted]	[redacted]	[redacted]	[redacted]
LDH excluded	[redacted]	[redacted]	[redacted]	[redacted]
Disease stage excluded	[redacted]	[redacted]	[redacted]	[redacted]
Scenario analysis (requested in the clarification questions)				
BRAF status included	[redacted]	[redacted]	[redacted]	[redacted]
BRAF status included and disease stage removed	[redacted]	[redacted]	[redacted]	[redacted]

ECOG PS - Eastern Cooperative Oncology Group Performance Status; HR - hazard ratio; LDH - lactate dehydrogenase; OS - overall survival; PFS - progression-free survival; STC - simulated treatment comparison

Figure 9: Adjusted (STC) and unadjusted Kaplan-Meier curves of PFS of lifileucel versus ipilimumab (reproduced from CS, Figure 12)

KM - Kaplan-Meier; PFS - progression-free survival; STC - simulated treatment comparison

Figure 10: Adjusted (STC) and unadjusted Kaplan-Meier curves of OS of lifileucel versus ipilimumab (reproduced from CS, Figure 13)

The shaded areas around each plot represent 95% confidence intervals
KM - Kaplan-Meier; OS - overall survival; STC - simulated treatment comparison

4.5.3 ITC for lifileucel versus chemotherapy (unadjusted)

The data used for the comparison of lifileucel and chemotherapy included pooled IPD ([redacted]) from both Cohort 2 and Cohort 4 for lifileucel and pseudo-IPD reconstructed from digitised survival curves for chemotherapy from Mangin *et al.*[30] (N=50). The CS[1] states that it was not feasible to perform a population-adjusted indirect comparison with only 50 patients included in the comparator study. No analysis has been performed to address the population imbalance in the comparison of lifileucel and chemotherapy.

A summary of the baseline patient and disease characteristics from Study C-144-01[28] and Mangin *et al.*[30] is presented in Table 27. In response to clarification question A29,[27] the company states that patients in Study C-144-01 appear to be fitter than patients in Mangin *et al.* based on a comparison of age, ECOG PS, disease stage, LDH levels and presence of metastases. On average, Study C-144-01 patients were younger and less frail based on median age ([redacted] years vs 68.25 years) and the proportion of patients with an ECOG score of 0 or 1 ([redacted] vs 39%). The proportion of Stage IIIcd/IVM1ab is at least 14% in Mangin *et al.* and the proportion of Stage IIIC/IV M1a/IV M1b in Study C-144-01 is between [redacted] and [redacted] depending on the disease stage of the [redacted] unknown patients. Study C-144-01 has a higher proportion of patients with normal LDH levels ([redacted] vs 23.8%) and a lower proportion of patients with brain metastases ([redacted] vs 64%).

Table 27: Summary of unadjusted baseline patient and disease characteristics in studies considered for the STC analysis (adapted from CS, Table 22)

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
0	[redacted]	16 (39.0)	
1	[redacted]		
≥2	[redacted]	25 (61.0)	

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?
			of 2 [redacted]
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	

ECOG - Eastern Cooperative Oncology Group; ICI - immune checkpoint inhibitor; IRC - Independent Review Committee; LDH - lactate dehydrogenase; NR - not reported; PD-(L)1 - programmed death (ligand) 1; SD - standard deviation; SSM - superficial spreading melanoma; STC - simulated treatment comparison; ULN - upper limit of normal

Unadjusted HRs were calculated using a Cox regression model without adjusting for the population differences. The unadjusted HRs were estimated to be [redacted]. Unadjusted Kaplan-Meier curves of lifileucel versus chemotherapy for PFS and OS are presented in Figure 11 and Figure 12, respectively. After inspection of the log-cumulative hazard plots, Schoenfeld residual plots, QQ plots and smoothed hazard rate plots for both PFS and OS, the company concludes that there is evidence suggesting a violation of the PH assumption and the AFT assumption and that independent model fitting approaches may be more appropriate for survival extrapolation. Overall, the EAG expects that had the company adjusted for age, ECOG, disease stage, LDH levels and presence of metastases, the relative treatment effect of lifileucel versus chemotherapy would be smaller than in the unadjusted analysis.

Figure 11: Unadjusted Kaplan-Meier curves of PFS of lifileucel versus chemotherapy (reproduced from CS, Figure 14)

Figure 12: Unadjusted Kaplan-Meier curves of OS of lifileucel versus chemotherapy (reproduced from CS, Figure 15)

4.5.4 ITC for lifileucel versus BSC

Due to the lack of available data representing BSC, outcomes for this comparator were modelled using assumptions (see Section 5.3).

4.6 Indirect treatment comparison: Critique of statistical methods

4.6.1 ITC for lifileucel versus ipilimumab (STC-adjusted)

To adjust for the population differences between Study C-144-01[28] and da Silva,[52] the company adopted an unanchored STC approach. The EAG has several concerns regarding the company's STC analyses:

(i) The EAG is concerned about the robustness of the STC results as the differences in the adjusted and the unadjusted HRs are largely caused by adjusting for the LDH levels. The adjustment of other variables including age, sex, disease stage, ECOG score, and BRAF status appear to have only a limited impact on the results.

(ii) The EAG has some concerns about the covariates included for the STC analysis. For an unanchored STC analysis, all effect modifiers and prognostic factors have to be adjusted for in order to obtain a reliable estimate of the relative treatment effect.

  (a) The CS has provided a list of variables that should be included for adjustment based on discussions with UK clinical experts. However, the EAG could not identify details of these discussions from the minutes of the clinical advisory board meeting.[26, 56]

  (b) The company has included five variables in their preferred base case STC analyses. BRAF status was observed in both studies but was not included in the adjustment. The EAG would prefer an analysis that adjusts for all observed effect modifiers and prognostic variables, including BRAF status.

  (c) The likely extent of error due to covariates not being unaccounted for is unknown. The residual bias due to unobserved prognostic factors and effect modifiers, including target lesion sum diameter and line of therapy, has not been quantified.

(iii) The EAG is unclear about the impact of the additional assumptions made in the process of simulating patient-level covariates matching the da Silva ipilimumab population. To address discrepancies in baseline characteristics reporting between the two included studies, the company employed some pragmatic data manipulation techniques. However, these may have introduced inconsistencies between the simulated population and the da Silva population, potentially adding further bias to the results.

(iv) Insufficient evidence has been provided on the assessment of the correct model specification, the overall fit of the model, or on the justification that absolute outcomes can be predicted with sufficient accuracy in relation to the relative treatment effects.

(v) A MAIC analysis has not been performed. The EAG acknowledges that a MAIC suffers from a large reduction in effective sample size when the degree of overlap in covariates is poor, but considers that such an analysis would provide further justification to the STC results. Such an

analysis may help to reduce the uncertainty around the direction and magnitude of the relative treatment effect of lifileucel versus ipilimumab.

(vi) The relative treatment effects were estimated in the da Silva population. It is unclear whether the adjusted HRs are applicable to the target population for this appraisal. The EAG considers that the ITC results should be interpreted with caution.

(vii) The company states that independent model fitting approaches may be more appropriate for survival extrapolation after providing evidence against the PH assumption and AFT assumption. However, the EAG notes that the company did not fit separate survival models to the STC-adjusted data.

4.6.2 ITC for lifileucel versus chemotherapy (unadjusted)

Due to the differences in baseline characteristics between Study C-144-01[28] and Mangin *et al.*,[30] the EAG considers that the unadjusted treatment effect is biased. As the Mangin population appears to be less fit in terms of age, ECOG PS, disease stage, LDH levels and presence of metastases, compared to the C-144-01 population, the EAG expects that the relative treatment effect after adjusting for age, ECOG PS, disease stage, LDH levels and presence of metastases would be smaller than the unadjusted effect. Thus, the EAG considers that that the unadjusted HR may overestimate clinical benefits for the comparison of lifileucel versus chemotherapy.

4.7 Conclusions of the clinical effectiveness section

The pivotal study (C-144-01)[28] is a multinational, Phase II, open-label, single-arm study designed to assess the efficacy and safety of the lifileucel regimen in adults (≥18 years) with unresectable or metastatic melanoma (Stage IIIC or Stage IV) who had received at least one prior systemic treatment, including a PD-1 inhibitor and, for those with a BRAF V600 mutation, a BRAF inhibitor with or without a MEK inhibitor. Patients underwent a three-step treatment regimen comprising LD chemotherapy (cyclophosphamide and fludarabine), a single lifileucel infusion, and high-dose IL-2 administration (up to six doses). Multiple analysis sets were presented. The FAS included 153 patients (87 from Cohort 4, 66 from Cohort 2), excluding those who received an out-of-specification infusion. The PDAwCS analysis set included [redacted] who received lifileucel within the proposed SmPC dosing range[12] and manufactured at facilities approved for commercial supply. This dataset formed the basis for the results used in the company's economic model. As of the 30th June 2023 DCO (median follow-up: [redacted]), pooled results from Cohorts 2 and 4 in the PDAwCS efficacy set demonstrated an ORR of [redacted], as assessed by an IRC using RECIST v1.1 criteria. CR was achieved in [redacted], PR in [redacted] and SD was observed in [redacted] patients. Median PFS, as assessed by the IRC, was [redacted], with a 1-year PFS rate of

[redacted], and a 4-year PFS rate of [redacted]. Median OS, as assessed by the investigators, was [redacted], with a 12-month OS rate of [redacted]. All patients in the SAS (N=156) experienced ≥1 TEAEs of any grade during the course of the study. The most common TEAEs (defined as AEs that occurred from the time of the lifileucel infusion to 30 days post-infusion) with an incidence of 20% or higher (any grade) were:

[redacted] The most common Grade 3/4 AEs were: [redacted]. The most common post-TEAEs (defined as AEs that began 30 days following lifileucel infusion and extended through 6 months post-infusion or until initiation of a new anticancer therapy, whichever occurred first) with an incidence of ≥5% were: [redacted] In general, the frequency and severity of most TEAEs were not unusual and were considered by the company and a US FDA clinical review[40] to be predictable and manageable based on the components of the regimen. The EAG's main key concern regarding the clinical evidence relates to the single-arm design of Study C-144-01, which is subject to inherent methodological limitations, including the absence of a control group, limited ability to adjust for confounding variables and an increased risk of bias, all of which may affect the reliability and interpretation of the results,[45-47] particularly in estimating the magnitude of treatment benefit. In addition, for widespread adoption in England, several key challenges need to be addressed (see clarification response,[27] question A1) including manufacturing capacity and product availability, scalability of production, logistical complexities, appropriate patient selection and the management of treatment-related toxicities.

Owing to the absence of head-to-head randomised studies, the company undertook ITCs comparing lifileucel versus ipilimumab and lifileucel versus chemotherapy. The company conducted an STC for the comparison of lifileucel and ipilimumab, with da Silva *et al.* (N=162) informing outcomes for ipilimumab. The adjusted HRs were estimated to be [redacted] suggesting a larger clinical benefit for lifileucel compared to the unadjusted HRs of [redacted]. For the comparison of lifileucel and chemotherapy, an unadjusted (naïve) ITC was presented,

with Mangin *et al.* (N=50) informing outcomes for chemotherapy. The unadjusted HRs were estimated to be [redacted]. The EAG is concerned about the robustness of the STC results as they are largely affected by adjusting for the difference in LDH levels, while the adjustment of other observed covariates has only a limited impact on the results. Given concerns regarding the covariates included for adjustment, the potential residual bias due to unobserved confounders, and the lack of sufficient evidence supporting the assessment of the model assumptions, the EAG considers that the STC-adjusted results should be interpreted with caution. The EAG is also concerned about the naïve ITC between lifileucel and chemotherapy as the chemotherapy patients in Mangin *et al.* appear to be less fit than the lifileucel population in Study C-144-01 given the reported baseline patient and disease characteristics.

5. COST EFFECTIVENESS

5.1 Summary and critique of the company's review of existing economic evaluations

The company undertook an SLR to identify existing cost-effectiveness analyses of treatments for adult patients with previously treated, unresectable or metastatic melanoma. The review presented in Section 3.1 of the CS[1] includes published model-based economic evaluations and previous NICE technology appraisals (TAs) of treatments for advanced melanoma. The company's full review presented in CS Appendix E[13] also includes a summary of cure modelling approaches applied in previous NICE TAs of chimeric antigen receptor T-cell (CAR-T) therapies for various haematological malignancies.

5.1.1 Summary and critique of company's searches

Search strategies for the economic evaluation SLRs are presented in CS Appendix E (cost-effectiveness), Appendix F (HRQoL) and Appendix G (cost and health care resource use [HCRU]).[13] In line with the clinical SLR, the searches were initially carried out in August 2024 and updated in January 2025 with no gap in coverage. However, as with the clinical SLR, a date limit of 2014 was applied. The company justified this in its response to clarification question A10[27] as a reasonable date cut-off because 2014 marked the introduction of PD-1 inhibitors, which changed the treatment landscape relevant to this submission. The EAG is unclear whether the 2014 cut-off will have led to the omission of relevant economic analyses of comparators.

As with the clinical SLR, the range of databases searched was incorrectly reported, whereby CS Appendix E.2.1,[13] states that Embase, MEDLINE and PubMED-not-MEDLINE were searched. The company's clarification response[27] (question A4) acknowledges the error and confirms that Embase.com was used to search Embase and the MEDLINE supplement available on this platform, which is reflected in the PRISMA diagrams in Figures 8-10 (clarification response, question A11).

It is unclear from the CS whether relevant economics-focused bibliographic databases had been searched as part of the non-clinical SLR. The company's response to clarification question A7[27] states that the University of York Centre for Reviews and Dissemination (CRD) database was searched, which includes the NHS Economic Evaluation Database (NHS EED) and the Database of Abstracts of Reviews of Effects (DARE), but that none of the results found from this source were included in the final review. The company's response also states that the International Health Technology Assessment (HTA) Database was searched via CRD, but records since 2018 have been held at inahta.org, so it remains unclear how thoroughly the International HTA database was searched as part of this SLR. In the reporting of the searches and screening in the PRISMA diagrams in Figures 8-10 of the CS appendices, it is not clearly reported that these sources were searched or at what stage the results from them were excluded.

A further error in search reporting in the CS relates to the titles of conference proceedings that were searched as part of supplementary methods. There was a discrepancy between the congresses listed (CS Appendix E.2.1,[13] pages 106-107, Appendix F.2.2, pages 130-131, and Appendix G.2.1, page 156). The company's response to clarification question A8[27] states that an appropriate range of conference proceedings were searched for all three of the economic reviews, as was the WHO-ICTRP.

The EAG also questioned the omission of the Health Technology Assessment International (HTAi) congress as a supplementary source for conference abstracts, especially given that the Professional Society for Health Economics and Outcomes Research (ISPOR) conference had been included. As part of its clarification response[27] (question A8), the company conducted additional searches of HTAi abstracts from 2022-2025, which produced no additional relevant results.

CS Appendices E.2.1., F.2.2 and G.2.1[13] mention that filters were used to ensure the search matched the respective review question, but the CS does not report whether published and validated search filters were used. The company's response to clarification question A9(b)[27] confirms that the filters for cost-effectiveness and HCRU studies used in the searches reported in Tables 17 and 32 of the CS[1] were based on work by SIGN (https://www.sign.ac.uk/using-our-guidelines/methodology/search-filters/). The filter for the HRQoL studies used in the searches reported in Table 25 of the CS was from Arber *et al.* 2015.[31] Whilst the company has provided the sources for the filters used, details of any modifications and justification for making these have not been provided. The EAG considers it best practice to use validated search filters without modification.

Overall, the EAG's concerns with the non-clinical SLRs are similar to those with the clinical SLR. In particular, the robustness in the search methodology is lacking because of the small range of bibliographic databases searched. Issues with the reporting, particularly of supplementary methods, further undermine the EAG's overall confidence in the literature search for the non-clinical review.

5.1.2 Summary and critique of the company's SLR of existing economic evaluations

The inclusion criteria for the company's SLR of existing economic evaluations are reported in CS Appendix E,[13] Table 16. Studies were eligible for inclusion in the review if the population included in the economic analysis related to adult patients with unresectable or metastatic melanoma (Stage IIIC, IIID or IV) who had been previously treated with a PD-1 blocking antibody and a BRAF +/- MEK inhibitor if BRAFV600 mutation-positive. Relevant interventions and comparators included: lifileucel; ipilimumab; chemotherapy (dacarbazine; temozolomide; carboplatin; cisplatin or paclitaxel) and BSC. Relevant study types included cost-effectiveness analyses, cost-utility analyses and budget impact analyses. Outcomes included incremental cost-effectiveness ratios (ICERs) reported in terms of the incremental cost per quality-adjusted life year (QALY) gained or the incremental cost per life year

gained (LYG), or budget impact. Full papers and abstracts were includable in the review. Studies were restricted to those published in the English language since 2014. The quality of published economic evaluation studies was assessed using the Drummond checklist;[60] the quality of models developed to inform NICE TAs was not assessed as part of the SLR.

The company's initial and updated bibliographic searches identified a total of 154 studies, of which three published economic evaluation studies were included in the review. A fourth published economic evaluation study was identified from the grey literature search. Additional searches of HTA websites and databases resulted in the inclusion of 12 NICE TAs of treatments for advanced melanoma and five NICE TAs of CAR-T therapies (the latter studies are not discussed further in this report). The identified economic analyses of treatments for advanced melanoma are summarised in Table 28, based on further examination of each included study by the EAG.

All of the 16 included economic analyses of treatments for advanced melanoma were model-based cost-utility analyses; none were budget impact analyses. None of the analyses include lifileucel. Amongst the four published economic studies, two reflect the Dutch health care setting, one reflects the Japanese setting, and one reflects the US setting. The EAG notes that whilst the company's reported inclusion criteria restrict the relevant population to patients who have received prior treatment, this criterion does not appear to have been applied consistently in the study selection process, as several included analyses reflect an untreated advanced melanoma population. Most of the included models adopted a partitioned survival approach, although the use of state transition models (mostly semi-Markov models) was also common. Most of the included models adopted structures which are comprised of three health states: (i) progression-free; (ii) progressed disease and (iii) dead. The survival modelling approaches applied in the models vary considerably, with cure sometimes being assumed for patients receiving certain therapies (particularly those receiving ipilimumab, nivolumab or pembrolizumab). None of the included studies modelled cure using mixture-cure models (MCMs). Rather, the included models appear to implicitly model cure either through the selection of parametric survival models which result in a long-term plateau (e.g., Gompertz distributions) or through the use of a structural cure assumption whereby general population mortality risks are assumed to take over after a specific time point since model entry. Standardised mortality ratios (SMRs) reflecting excess mortality risks are included in some of the economic analyses but not others. Several NICE TAs have applied hybrid piecewise models for long-term OS informed by empirical trial-based survival, some extrapolation of trial data and external data (including data from registry analyses).

Table 28: Summary of studies included in the company's review of existing economic evaluations

Study	Analysis type	Setting	Population	Intervention / comparators	Model type (states)	Cure assumptions included in model
Published full economic evaluations						
Retel *et al.*[61]	CUA	Netherlands	2L metastatic melanoma	TIL Ipilimumab	3-state Markov model (SD, PD, dead)	Not reported. The model does not appear to include potential for cure.
Ten Ham *et al.*[62]	CUA	Netherlands	2L or 3L unresectable Stage IIIc-IV melanoma	TIL-NKI/CCIT Ipilimumab	Decision tree + 3-state Markov model (PF, PD, dead)	Cure not explicitly modelled. The model applies standard log-logistic survival models for PFS and OS in both treatment groups.
Paly *et al.*[63]	CUA	Japan	1L advanced melanoma	Nivolumab + ipilimumab Nivolumab Ipilimumab	3-state PartSA (PF, PD, dead)	PFS and OS modelled using standard parametric survival distributions. PFS and OS for nivolumab + ipilimumab based on Gompertz model which appears to feature a long-term plateau, thereby suggesting cure for this group only.
Curl *et al.*[64]	CUA	US	BRAF+ metastatic melanoma	Dacarbazine Vemurafenib Vemurafenib + ipilimumab	Decision tree	Not reported. The model does not appear to include potential for cure.
Previous NICE TAs of treatments for advanced melanoma						
TA268[65]	CUA	England	Previously treated advanced melanoma	Ipilimumab BSC	4-state PartSA (baseline disease, non-progressive disease, PD, dead)	PFS and OS modelled using standard parametric survival models. The model includes a structural assumption of cure after 5 years.
TA269[15]	CUA	England	1L $BRAF^{V600}$ mutation-positive metastatic melanoma	Vemurafenib Dacarbazine	3-state PartSA (PF, PD, dead)	OS is modelled using a hybrid approach including use of SEER data after Month 46. The model includes a constraint which allows general population mortality to take over if this exceeds the mortality risk from SEER (thereby implying cure). It is unclear whether this implicit cure assumption impacts on the results.
TA319[16]	CUA	England	1L advanced melanoma	Vemurafenib Ipilimumab	5-state semi-Markov (1L therapy, 2L	Not reported. The model does not appear to explicitly include the potential for cure.

Study	Analysis type	Setting	Population	Intervention / comparators	Model type (states)	Cure assumptions included in model
			(split by $BRAF^{V600}$ subgroups)	Dacarbazine	therapy, 3L therapy, palliative care, dead)	Mortality risks after 3 years are informed by external data from the AJCC registry.
TA321[17]	CUA	England	1L $BRAF^{V600}$ mutation-positive metastatic melanoma	Dabrafenib Vemurafenib Dacarbazine	3-state PartSA (PF, PD, dead)	The model includes a structural assumption of cure for patients who survive up to 10 years. Beyond this time point, mortality risks are informed by general population life tables (the use of an SMR is not mentioned).
TA357[18]	CUA	England	Advanced melanoma, previously treated with ipilimumab	Pembrolizumab Chemotherapy/BSC	3-state PartSA (PF, PD, dead)	OS is modelled using a hybrid approach, including the use of external registry data for patients surviving up to Year 11. The model includes a constraint which allows general population mortality to take over if this exceeds the mortality risk from the registry data (thereby implying cure). It is unclear whether this implicit cure assumption impacts on the results.
TA366[19]	CUA	England	Advanced melanoma, ipilimumab-naïve (split by $BRAF^{V600}$ subgroups)	Pembrolizumab + ipilimumab Vemurafenib Dabrafenib	3-state PartSA (PF, PD, dead)	OS is modelled using a hybrid approach, including the use of external registry data for patients surviving to 10 years. General population mortality risks were added to the risks obtained from the registry, thereby not implying cure.
TA384[66]	CUA	England	1L advanced melanoma (split by $BRAF^{V600}$ subgroups)	Nivolumab Ipilimumab Dacarbazine Ipilimumab Vemurafenib Dabrafenib	3-state semi-Markov (PF, PD, dead)	Standard parametric survival models were fitted to trial and registry data. The models selected for inclusion in the base case analysis suggest a plateau for nivolumab and ipilimumab, but not for the other comparators.
TA400[21]	CUA	England	1L advanced melanoma	Nivolumab + ipilimumab Ipilimumab Vemurafenib	3-state semi-Markov (PF, PD, dead)	The model uses external data from Schadendorf *et al.*[58] beyond Year 3 which leads to an apparent plateau in OS for

Study	Analysis type	Setting	Population	Intervention / comparators	Model type (states)	Cure assumptions included in model
				Dabrafenib		nivolumab + ipilimumab and ipilimumab, but not for the other comparators.
TA396[20]	CUA	England	Patients with $BRAF^{V600}$ mutation-positive advanced melanoma	Trametinib + dabrafenib Dabrafenib Vemurafenib	3-state PartSA (PF, PD, dead)	After 20 years, mortality risk is modelled using general population mortality rates uplifted using a mortality ratio of 1.4.
TA410[67]	CUA	England	Non-visceral metastatic melanoma (stage IIIB to stage IV M1a disease	Talimogene laherparepvec Ipilimumab	3-state PartSA (non-progressive disease, PD, dead)	OS is modelled using a 4-phase hybrid approach based on: Kaplan-Meier estimates, an exponential function, external registry data and general population life tables. The model applies a structural assumption of cure for people surviving up to 10 years.
TA562[22]	CUA	England	Advanced $BRAF^{V600}$ mutation-positive melanoma (treatment line not clearly specified)	Encorafenib + binimetinib Dabrafenib + trametinib	3-state model (model type unclear; PF, PD, dead). Tunnel states used to account for patients being on/off treatment in both alive states.	OS is modelled using a hybrid approach based on Kaplan-Meier estimates, external registry data and general population life tables. The model applies life table risks after 20 years, uplifted using a multiplier of 2.2.
TA950[24]	CUA	England	1L advanced melanoma	Nivolumab + relatlimab, Nivolumab, Nivolumab + ipilimumab Pembrolizumab	3-state PartSA (non-progressive disease, PD, dead)	The model uses Gompertz survival models for PFS and OS in the nivolumab + relatlimab and nivolumab groups which include plateaus. This means that some patients eventually have no risk of progression or death due to melanoma.

CUA - cost-utility analysis; PartSA - partitioned survival analysis; AJCC - American Joint Committee on Cancer; SMR - standardised mortality ratio; 1L - first-line; 2L - second-line; 3L - third-line; SD - stable disease; PF - progression-free; PD - progressed disease; TIL - tumour infiltrating lymphocytes; TIL-NKI CCIT - ex vivo-expanded tumour infiltrating lymphocytes; PFS - progression-free survival; OS - overall survival; SEER - Surveillance, Epidemiology, and End Results

5.2 Summary of the company's submitted economic model by the EAG

This section provides a detailed description of the methods and results of the original version of the company's economic model, as described in the CS.[1] Following the clarification process, the company submitted a revised version of the model which includes the correction of errors identified by the EAG. The company's updated model and its results are summarised separately in Section 5.4.

5.2.1 Scope of the company's economic analysis

As part of its submission to NICE,[1] the company submitted an executable health economic model programmed in Microsoft Excel.® The company's base case analysis compares lifileucel versus ipilimumab, chemotherapy and BSC for adult patients with previously treated, unresectable or metastatic melanoma. The scope of the company's economic analysis is summarised in Table 29.

Table 29: **Scope of the company's economic analyses**

Population	[redacted]
Time horizon	Lifetime ([redacted] years)
Intervention	Lifileucel (AMTAGVI®)
Comparator	• Ipilimumab • Chemotherapy • BSC
Type of economic analysis	Cost-utility analysis
Outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Discount rate	3.5% per annum in base case (1.5% explored in scenario analysis)
Price year	2023/2024 (except for drugs which reflect current prices)

MEK - mitogen-activated protein kinase; BSC - best supportive care; QALY - quality-adjusted life year; NHS - National Health Service; PD-(L)1 - programmed death (ligand) 1; PSS - Personal Social Services

The model assesses the cost-effectiveness of lifileucel versus each of the three comparators (ipilimumab, chemotherapy and BSC) in terms of the incremental cost per QALY gained. The economic analysis was undertaken from the perspective of the NHS and Personal Social Services (PSS) over a lifetime time horizon ([redacted] years). Unit costs are valued at 2023/24 prices, except for drug acquisition costs which are valued at 2025 prices. Health outcomes and costs are discounted at a rate of 3.5% per annum in the base case analysis, with alternative discount rates of 1.5% explored as part of the scenario analyses (see Section 5.2.6).

Population

The population included in the company's economic model reflects the characteristics of patients in Cohorts 2 and 4 in the PDAwCS efficacy set from Study C-144-01.[28] At model entry, patients are

assumed to have a mean age of [redacted] years. Other patient characteristics used in the model are described in Section 5.2.4.1.

Interventions

The intervention evaluated within the model is lifileucel, which is administered as a single IV infusion at a dose of [redacted] viable cells. Further details of the four phases of the lifileucel regimen can be found in Section 3.2. Costs of the individual regimen components are described in Section 5.2.4.5.

Comparators

The company's economic analysis includes three comparators: (i) ipilimumab monotherapy, (ii) chemotherapy, and (iii) BSC.

Ipilimumab is assumed to be administered as an IV infusion at a dosage of 3mg/kg over a 30-minute period every 3 weeks for a maximum of 4 doses. This is in line with the SmPC for ipilimumab.[68] The company's model assumes that patients will receive ipilimumab for a mean duration of 3.6 doses, based on the proportion of patients (64.2%) who received the maximum number of doses in the ipilimumab monotherapy group in the RCT reported by Hodi *et al.*[69] The company explored the impact of all patients receiving all 4 doses of ipilimumab in a scenario analysis (see Section 5.2.6.4).

The chemotherapy treatment group is modelled as a basket of therapies which includes five chemotherapy regimens: (i) dacarbazine monotherapy; (ii) temozolomide monotherapy; (iii) carboplatin monotherapy; (iv) carboplatin plus paclitaxel and (v) dacarbazine plus cisplatin. The weights applied to each chemotherapy regimen are based on clinical opinion obtained during an advisory board meeting held by the company[26] (dacarbazine 65%, temozolomide 10%, carboplatin 5%, carboplatin plus paclitaxel 10%, and dacarbazine plus cisplatin 10%). All regimens are assumed to be administered via IV infusion/injection, except for temozolomide, which is administered orally. The dosing schedule for each regimen is summarised in Section 5.2.4.5. The model assumes that all chemotherapy regimens have equivalent efficacy, and the CS[1] does not include economic comparisons for lifileucel against each individual chemotherapy regimen. The model assumes that all chemotherapy regimens are administered for a fixed duration of 1.49 months, based on the median treatment duration reported in Mangin *et al.*[30]

The EAG notes that there are some differences between the chemotherapy regimens listed in the final NICE scope[29] and those included in the chemotherapy comparator group of the company's model. The model excludes paclitaxel monotherapy but includes carboplatin monotherapy and dacarbazine plus cisplatin which are not listed in the NICE scope. However, the EAG considers these to be minor discrepancies which are likely to have only a limited impact on the model results.

The company's model also includes BSC as a comparator. The CS[1] (page 123) defines BSC as symptom and disease management which includes *"palliative care, radiotherapy, and emotional and practical support."* The CS states that BSC is currently recommended for patients for whom ipilimumab, pembrolizumab, nivolumab, and targeted therapies would be contraindicated. However, the EAG's clinical advisors noted that most of the target population for this appraisal currently receive BSC at 2L or 3L (if BRAF V600 mutation-positive), since patients would already have received previous treatment with ipilimumab plus nivolumab (and BRAF+-MEK inhibitor if BRAF+) if eligible, and because chemotherapy is associated with limited efficacy and additional toxicity. The EAG's clinical advisors also noted that some patients are enrolled in clinical trials, where eligible.

5.2.2 Model structure

The structure of the company's model is described in Section 3.2.2 of the CS.[1] The company describes their approach as a partitioned survival model. However, the EAG notes that the model also includes an initial decision tree component within the lifileucel group; this decision tree governs whether patients receive the lifileucel infusion, and the costs and outcomes accrued by patients who do or do not receive the infusion (see Figure 13).

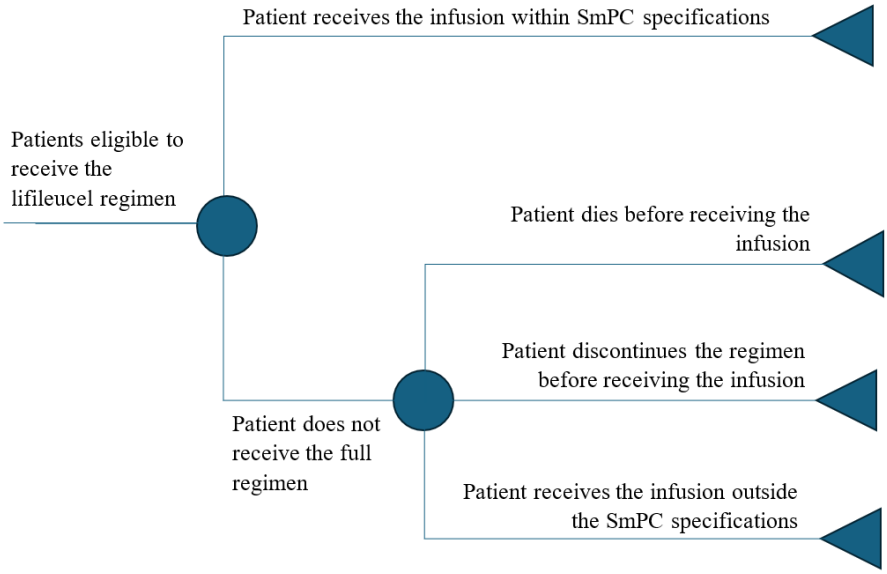
Decision tree component

Patients for whom the lifileucel infusion is planned may: (i) receive the lifileucel infusion manufactured within the SmPC specifications ([redacted] of patients who underwent tumour tissue procurement 'with lifileucel manufactured at a commercially approved manufacturing site' in Study C-144-01;[28] see clarification response,[27] question B10); (ii) receive the infusion outside of the specifications ([redacted] of patients); (iii) discontinue the lifileucel regimen before receiving the lifileucel infusion ([redacted] of patients) or (iv) die before they receive the lifileucel infusion ([redacted] of patients). Patients in the lifileucel group who receive a within-specification lifileucel infusion are assigned the costs and outcomes associated with the lifileucel regimen. Patients who discontinue the regimen or receive the infusion outside of the specifications are assigned part of the lifileucel regimen treatment costs (see Section 5.2.4.5), whilst their health outcomes and costs are assumed to be derived from a 'standard care' comparator based on a weighting of the three individual comparators (ipilimumab [redacted], chemotherapy [redacted], and BSC [redacted]).[70] Patients who die before receiving the lifileucel infusion are assigned only the costs associated with the surgical resection of tumour tissues and end-of-life care (see Section 5.2.4.5).

The CS[1] comments that: "*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."

Figure 13: **Company's decision tree structure for patients in whom the lifileucel infusion is planned**



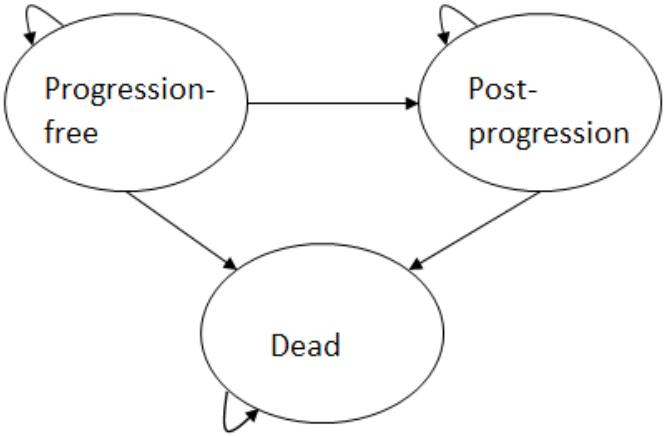
SmPC - Summary of Product Characteristics

Partitioned survival model component

The partitioned survival component of the model applies to all treatment groups and is comprised of three mutually exclusive and jointly exhaustive health states: (i) progression-free; (ii) progressed disease and (iii) dead (see Figure 14). The incremental health gains, costs and cost-effectiveness for lifileucel versus ipilimumab, chemotherapy and BSC are estimated over a lifetime ([redacted] years) horizon using weekly cycles. The model does not include half-cycle correction due to the short cycle length.

The model logic for the partitioned survival model operates as follows. Patients enter the model in the progression-free state and receive treatment with either lifileucel (following the decision tree outcomes described above), ipilimumab, chemotherapy or BSC. At any time *t*, health state occupancy is determined by the cumulative probabilities of OS and PFS, whereby: the probability of being alive and progression-free is given by the cumulative probability of PFS; the probability of being alive following disease progression is calculated as the cumulative probability of OS minus the cumulative probability of PFS, and the probability of being dead is calculated as one minus the cumulative probability of OS. Patients in all treatment groups are assumed not to receive any further active treatment after disease progression (i.e., they receive BSC alone).

Figure 14: **Company's partitioned survival model structure**



The cumulative probabilities of PFS and OS for patients receiving lifileucel are modelled using MCMs fitted to time-to-event data from the PDAwCS efficacy set from Study C-144-01 (DCO 30th June 2023).[28] In the comparison against ipilimumab, the MCMs for lifileucel are uplifted using the ratio of STC-adjusted and unadjusted HRs (see Section 4.5), whereas in the comparisons against chemotherapy and BSC, the MCMs for lifileucel are not adjusted. PFS and OS for patients receiving ipilimumab and chemotherapy are modelled using standard parametric models fitted to data from da Silva *et al.*[52] and Mangin *et al.*,[30] respectively, whilst PFS and OS for patients receiving BSC are modelled by raising the survival models for chemotherapy by an HR of 2.0. The economic model applies a structural constraint which ensures that the per-cycle risk of death in the targeted population cannot be lower than that in the age- and sex-matched general population. The model applies a further constraint which ensures that the cumulative probability of PFS cannot be higher than the cumulative probability of OS at any time point. The model also includes an assumption that lifileucel-treated patients who are cured and ipilimumab-treated patients who are still alive and progression-free at 3 years incur the same risk of death as the age- and sex-matched general population (with an SMR of 1.0 assumed in the company's base case).

HRQoL is assumed to be determined by the presence/absence of disease progression, with the same utility values applied to the health states for all treatment groups. The model assumes that lifileucel- and ipilimumab-treated patients who remain alive and progression-free at 3 years are cured; hence, their HRQoL rebounds to general population levels at this time point. Utility values are adjusted for increasing age. The model also includes short-term QALY losses associated with: (i) lifileucel administration (lifileucel treatment group only) and (ii) Grade ≥3 TEAEs which occurred in ≥5% of patients in Study C-144-01,[28] da Silva *et al.*[52] or Mangin *et al.*[30] No TEAEs are assumed for patients receiving BSC. TEAEs are assumed to have a negative HRQoL impact for a duration of one week.

The model includes costs associated with: (i) drug acquisition and administration (including tumour procurement, pre- and post-infusion treatments for patients in the lifileucel group); (ii) health state management (scans, tests and clinic visits); (iii) the management of AEs and (iv) end-of-life care costs. Drug acquisition and administration costs for lifileucel and chemotherapy are applied as once-only costs in the first model cycle, whilst for ipilimumab these costs are applied for the duration of the treatment. Drug acquisition costs are modelled as a function of the drug price (including the PAS discount for lifileucel and list prices for all other drugs), the treatment schedule, the treatment duration and RDI, and include assumptions around wastage. Health state costs are applied in each model cycle. TEAEs costs and end-of-life care costs are applied once-only at the first cycle and at the point of death, respectively.

All ICERs presented in the CS[1] are pairwise comparisons of lifileucel versus each comparator; a fully incremental analysis is not presented. All ICERs included in the CS include severity weighting applied to the incremental QALY gains.

5.2.3 Key assumptions employed in the company's model

The company's economic model employs the following key assumptions:

- Ipilimumab, BSC and chemotherapy are all comparators for lifileucel. Chemotherapy is represented as a basket of therapies (dacarbazine; temozolomide; carboplatin; carboplatin plus paclitaxel and dacarbazine plus cisplatin).
- Following disease progression, patients are assumed to receive BSC only.
- [redacted] of patients in whom lifileucel infusion is planned will discontinue or die before receiving the infusion or will receive an out-of-specification dose. Patients who receive an out-of-specification dose or discontinue the lifileucel regimen are assumed to go on to receive a mix of the comparator therapies.
- For the comparison of lifileucel versus ipilimumab, the model uplifts the PFS and OS survivor functions for the lifileucel group by the STC-adjusted HR for lifileucel versus ipilimumab divided by the unadjusted HR for lifileucel versus ipilimumab. This approach assumes that if lifileucel was used in the da Silva *et al.* ipilimumab population,[52] PFS and OS outcomes for lifileucel would be improved compared with those observed in the Study C-144-01 population.[28]
- The model includes two main structural constraints: (i) the risk of death in people with advanced melanoma must be at least as high as that in the general population, and (ii) the cumulative PFS probability cannot be higher than the cumulative OS probability.
- Lifileucel is assumed to be curative for a proportion of patients. PFS is modelled using a log-normal MCM and OS is modelled using an exponential MCM. The STC-adjusted MCMs for PFS and OS imply higher cure fractions for lifileucel compared with the unadjusted MCMs.
- Lifileucel patients who are cured are assigned an SMR of 1.0 (i.e., no excess risk of mortality).

- Ipilimumab and chemotherapy are modelled using standard parametric models which do not allow for the possibility of cure. For both of these comparators, PFS is modelled using standard log-logistic models and OS is modelled using standard log-normal models. An adjustment is applied to the log-normal OS survival model for the ipilimumab group to allow for cure in the [redacted] of patients who are predicted to remain alive and progression-free at 3 years.
- The risks of progression and death for patients receiving BSC are assumed to be twice as high as those for chemotherapy. This is applied by applying an HR of 2.0 to the PFS and OS the chemotherapy models.
- HRQoL is determined by the presence/absence of disease progression. A higher utility value is applied to patients who are progression-free compared with those who have progressed disease. Patients in the lifileucel and ipilimumab groups who remain progression-free at 3 years are assumed to rebound to general population HRQoL.
- HRQoL is adjusted for increasing age, based on general population Euroqol 5-Dimensions 3-Level (EQ-5D-3L) estimates reported by Hernandez Alava *et al.*[71]
- All AEs are assumed to occur in the first model cycle and persist for one week. AEs result in QALY losses and incur additional costs. No AEs are included for BSC. The model includes an additional QALY loss associated with the administration of lifileucel which is assumed to last for one week.
- The model assumes that the NHS only bears the cost of lifileucel if the patient receives the infusion in line with commercial specifications. In instances whereby the patient does not receive the infusion or receives an out-of-specification dose, the NHS does not bear the cost of the infusion, but may bear the costs of other components of the overall regimen (see Section 5.2.4.5).
- The model includes the costs of follow-up for all patients. Patients who remain progression-free at 3 years in the lifileucel and ipilimumab groups are assumed to incur no further follow-up costs.
- All drug acquisition and administration costs for ipilimumab and chemotherapy are applied in the first 3 months of the time horizon. No drug costs are included for BSC.

- The company's QALY shortfall analysis suggests a decision modifier of 1.2 for the comparison of lifileucel versus ipilimumab and 1.7 for the comparison of lifileucel versus BSC and chemotherapy. The company's model applies a decision modifier of 1.7 for all comparisons. This higher decision modifier is reflected in all of the model results presented in the CS.[1]

5.2.4 Evidence used to inform the company's model parameters

Table 30 summarises the evidence sources used to inform the model parameter values. The evidence sources and the derivation of the parameter values are described in detail in the subsequent sections.

Table 30: **Evidence used to inform the model parameters**

Parameter/Group	Lifileucel	Ipilimumab	Chemotherapy	BSC
Patient characteristics	Study C-144-01[28]			
OS	Exponential MCM fitted to data from Study C-144-01[28] (DCO 30th June 2023). MCM function uplifted using HRs from ITC for comparison compared against ipilimumab only.	Standard log-normal model fitted to data from da Silva *et al.*[52]	Standard log- normal model fitted to data from Mangin *et al.*[30]	Chemotherapy OS model with HR of 2.0
PFS	Log-normal MCM fitted to data from Study C-144-01[28] (DCO 30th June 2023). MCM function uplifted using HRs from ITC for comparison compared against ipilimumab only.	Standard log-logistic model fitted to data from da Silva *et al.*[52]	Standard log-logistic model fitted to data from Mangin *et al.*[30]	Chemotherapy PFS model with HR of 2.0
AE frequencies	Study C-144-01[28]	da Silva *et al.*[52]	Mangin *et al.*[30]	Assumed to be zero
General population mortality	ONS life tables[72] (SMR = 1.0 applied to cured patients)			
Utility values for PF and PD health states	Unweighted mean of PF and PD utility values used in previous economic models of melanoma in the literature and previous NICE TAs (Retel *et al.*,[61] ten Ham *et al.*,[62] TA268,[65] TA269,[15] TA319,[16] TA321,[17] TA357,[18] TA366,[19] TA400[21] and TA562[22])			
Disutility lifileucel administration	Sung *et al.*,[73] Kelly *et al.*,[74] expert clinical opinion[26]	N/a	N/a	N/a
General population HRQoL	Hernández Alava *et al.*[71]			
Lifileucel decision tree probabilities	Probabilities derived from the number of patients in the FAS population for Cohorts 2 and 4 in Study C-144-01[28] (N=153) who either received lifileucel within specification (the PDAwCS population) or outside of specifications, or discontinued or died before receiving the lifileucel regimen	N/a	N/a	N/a
Treatment acquisition costs	List price and PAS discount provided by company, NHS Reference Costs 2023/24†,[75] C-144-01 trial,[28] mesna	Ipilimumab SmPC,[68] Study C-144-01,[28] BNF,[77] Hodi *et al.*,[69] and assumptions	SmPCs,[79-83] C-144-01 study,[28] FDA,[84] Gogas *et al.*,[85] Lee *et al.*,[86] Mangin *et al.*,[30] BNF[77] and eMIT[78]	Assumed to be zero

Parameter/Group	Lifileucel	Ipilimumab	Chemotherapy	BSC
	SmPC,[76] BNF,[77] eMIT[78] and assumptions			
Treatment administration costs	NHS Reference Costs 2023/24,[75] company's clinical expert opinion.[26]	NHS Reference Costs 2023/24,[75] Hodi *et al.*[69] with assumptions	NHS Reference Costs 2023/24[75] and assumptions	Assumed to be zero
Health care resource use in PF and PD states	Resource use frequency based on TA400.[21] Unit costs taken from NHS Reference Costs 2023/24[75]and PSSRU.[87]			
AE management costs	Unit costs taken from NHS Reference Costs 2023/24,[75] PSSRU,[87] TA893,[88] TA366,[19] TA950,[89] TA319,[16] Lorigan *et al.*[90] and company's advisory board meeting.[26]			
End-of-life care costs	Round *et al.*[91]			

BSC - best supportive care; OS - overall survival; PFS - progression-free survival; HRQoL - health-related quality of life; DCO - data cut-off; FAS - Full Analysis Set; MCM - mixture-cure model; HR - hazard ratio; ITC - indirect treatment comparison; SMR - standardised mortality ratio; PF - progression-free; PD - progressed disease; AE - adverse event; PSSRU - Personal Social Services Research Unit; ONS - Office for National Statistics.

† The EAG notes that whilst the company included the costs of tumour tissue procurement as part of administration costs, the EAG considers it as a separate procedure, and therefore it is included it as part of the treatment acquisition costs.

5.2.4.1 Patient characteristics

At model entry, patients are assumed to be [redacted] years of age and [redacted] of patients are assumed to be female. Patients are assumed to have a mean weight of [redacted] and a mean body surface area (BSA) of [redacted]. These characteristics reflect the population of patients in the PDAwCS efficacy set of Study C-144-01.[28] The weight and BSA distributions from the trial are used to estimate treatment dosages and consequently treatment costs for ipilimumab, chemotherapy regimens (dacarbazine, temozolomide, and cisplatin), and drugs used in the LD regimen for patients receiving lifileucel (cyclophosphamide, mesna and fludarabine).

5.2.4.2 Time to event parameters

5.2.4.2.1 Summary of company's parametric survival model fitting and selection process

The company fitted parametric survival models to the data on PFS and OS for patients receiving the lifileucel infusion from Study C-144-01[28] (DCO 30th June 2023). PFS and OS data for the comparator groups were taken from da Silva *et al.*[52] for ipilimumab and Mangin *et al.*[30] for chemotherapy. The CS[1] states that no suitable and up-to-date data sources were identified for BSC; outcomes for this group were instead modelled by applying an HR to the chemotherapy survival models. Six standard parametric survival models were fitted independently to the available PFS and OS data for each treatment group. These included the exponential, Weibull, Gompertz, log-normal, log-logistic, and generalised gamma distributions. These standard parametric survival models each assume a single homogeneous population. The company also fitted MCMs to the PFS and OS data from Study C-144-01 for the lifileucel group – these models assume that the population is comprised of two discrete patient groups: (i) patients who are cured who will not progress or die from their disease; and (ii) patients who are not cured and who have a continued risk of progression and/or death due to their disease. The proportion of patients who are cured is determined by the cure fraction, which is estimated through the model-fitting procedure. Six MCMs, analogous to those listed above for the standard parametric case, were fitted to the available PFS and OS data for the lifileucel group; however, the CS[1] states that the generalised gamma MCM did not converge. The fitted MCMs all assume an SMR of 1.0 (i.e., there is no excess risk of death for cured patients over and above the risk in the general population). MCMs were not fitted to the PFS or OS data for the ipilimumab and chemotherapy comparator groups. Standard parametric survival distributions were fitted to the data for the lifileucel group; however, these are not presented here as they were not used in either the company's base case or scenario analyses.

The company's model selection process included: (i) examination of the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) to assess relative goodness-of-fit between the models; (ii) visual inspection of the fitted models against the observed time-to-event data; and (iii) clinical plausibility of the models.

Due to differences in patient characteristics between the lifileucel and ipilimumab groups, the company carried out an adjusted survival analysis for the comparison of lifileucel versus ipilimumab, based on the STC for PFS and OS (see Section 4.5). In each case, the adjusted HR from the STC for lifileucel versus ipilimumab survival was divided by the unadjusted HR for lifileucel versus ipilimumab survival to estimate STC-adjusted lifileucel survival. The adjusted lifileucel PFS and OS curves were then obtained by raising the unadjusted lifileucel MCMs to the power of the ratio of STC-adjusted and unadjusted HRs. The CS[1] states that the alternative approach of raising the ipilimumab survival curves to the power of the STC-adjusted HR was not implemented because the shape and tail of the lifileucel survival curve would not be maintained (because MCMs were not fitted to the ipilimumab comparator group). In addition, the CS states that an adjusted survival analysis for lifileucel versus chemotherapy was not feasible due to the patient characteristics in Mangin *et al.* not being sufficiently similar to those in Study C-144-01.[28] As such, the company's base case model uses survival analyses which reflect two separate sets of comparisons: (i) an STC-adjusted comparison of lifileucel versus ipilimumab; and (ii) a naïve comparison of lifileucel versus chemotherapy and BSC.

Considerations of the clinical plausibility of the fitted survival models were informed by input from five UK clinical experts who were NHS consultant oncologists specialising in melanoma. The company held an advisory board meeting with the clinical experts.[26] One objective of this meeting was to obtain feedback on the clinical plausibility of survival outcomes predictions from the company's model for the UK melanoma population. The clinical experts provided estimates for the proportion of patients achieving long-term survival based on which treatment they received and commented on the company's presented survival analysis. The advisory board meeting was followed by one-to-one meetings with two of the clinical experts which were used to inform the company's model selection for the base case analysis.[70]

5.2.4.2.2 Progression-free survival (PFS)

PFS for patients receiving the lifileucel infusion was estimated using IPD from Study C-144-01;[28] the survival analysis was conducted using pooled data for Cohorts 2 and 4 from the PDAwCS efficacy set. PFS for patients receiving ipilimumab and chemotherapy was estimated from PFS data from da Silva *et al.*[52] and Mangin *et al.*,[30] respectively. Pseudo-IPD from these studies were generated using the algorithm reported by Guyot *et al.*[92] No data were available on PFS for patients receiving BSC; instead, PFS for BSC was obtained by applying an HR of 2.0 to the fitted survival models for chemotherapy.

AIC and BIC statistics for the parametric survival models fitted to the PFS data for lifileucel, ipilimumab and chemotherapy are shown in Table 31.

Table 31: AIC and BIC values for models of PFS

Model	Lifileucel (unadjusted)		Ipilimumab		Chemotherapy		BSC	
Mixture-cure-models	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential MCM	[redacted]		MCMs were not considered for ipilimumab, chemotherapy or BSC.					
Weibull MCM								
Gompertz MCM								
Log-normal MCM*								
Log-logistic MCM								
Generalised gamma MCM	N/a - did not converge.							
Standard models	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	Standard models are not considered in the company's base case. AIC and BIC values are available from the CS.[1]		734.21	737.29	194.46	196.38	Not applicable for BSC.	
Weibull			736.13	742.30	194.77	198.60		
Gompertz			725.89	732.06	195.83	199.65		
Log-normal			695.36	701.53	184.13	187.95		
Log-logistic†			**688.72**	**694.89**	**182.86**	**186.69**		
Generalised gamma			692.75	702.01	184.15	189.89		

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; PFS - progression-free survival; MCM - mixture-cure model; BSC - best supportive care; CS - company's submission
The AIC / BIC values of the best-fitting model are highlighted in bold.
** Model selected for PFS for lifileucel in company's base case.*
† Model selected for PFS for all comparators in company's base case.

Lifileucel PFS, unadjusted

The CS[1] states that a plateau in the observed PFS data for lifileucel in Study C-144-01[28] suggests a curative effect and none of the standard parametric survival models are able to capture this change in the hazard function. The CS states that the use of MCMs for lifileucel PFS was supported by the clinical experts who attended the advisory board meeting.[26] AIC and BIC statistics for the MCMs fitted to the lifileucel PFS data are shown in Table 31. Comparisons of model-predicted versus observed PFS are presented in Figure 15. Estimated cure fractions from the lifileucel MCMs for PFS are presented in Table 32. A comparison of smoothed empirical and model-predicted hazards for the lifileucel log-logistic MCM for PFS which was selected for inclusion in the company's base case model is presented in Figure 16.

Figure 15: Kaplan-Meier plots and fitted MCMs, PFS, lifileucel-infused population, Study C-144-01, unadjusted (generated using the company's model)

PFS - progression-free survival; KM - Kaplan-Meier
Includes general population mortality risks

Table 32: Estimated cure fractions for lifileucel for PFS

Mixture cure-models	Cure fraction estimated using MCM	Implied cure fraction after STC adjustment†
Exponential MCM	[redacted]	[redacted]
Weibull MCM	[redacted]	[redacted]
Gompertz MCM	[redacted]	[redacted]
Log-normal MCM*	[redacted]	[redacted]
Log-logistic MCM	[redacted]	[redacted]
Generalised gamma MCM	N/a - did not converge	

PFS - progression-free survival; STC - simulated treatment comparison; MCM - mixture-cure model; N/a - not applicable
** Model selected for OS for lifileucel in company's base case*
† Estimated by including the STC-adjusted HR and removing general population mortality risks from the MCM

Figure 16: Comparison of the observed and predicted PFS hazards for Study C-144-01 and log-logistic MCM (reproduced from CS, Figure 20)

MCM - mixture cure modelling; OS - overall survival; PFS - progression-free survival
Note: General population OS hazards represent US life tables

Amongst the MCMs fitted to the PFS data for the lifileucel group, the log-logistic distribution is the best-fitting model according to both the AIC and BIC; the log-normal MCM provides a similar fit. All MCMs provide a generally good visual representation of the observed data (see Figure 15). The cure fraction for lifileucel PFS across the MCMs ranges from [redacted] to [redacted]. Amongst the three best-fitting models, the exponential MCM has the highest cure fraction ([redacted]), whilst the cure fractions estimated by the log-normal and log-logistic MCMs are lower ([redacted] and [redacted], respectively). The CS[1] states that the log-normal MCM was selected for inclusion in the base case model for lifileucel PFS following one-to-one meetings with two clinical experts. However, the EAG notes that the minutes of these meetings indicate that one clinician was unable to select a most plausible survival distribution whilst the other expert expressed a preference for the log-logistic distribution. The log-logistic MCM and exponential MCM were used in the company's scenario analyses (see Section 5.2.6).

Lifileucel PFS, adjusted

As noted above, the company did not fit MCMs to the adjusted PFS data for lifileucel; rather, the unadjusted MCMs were uplifted using the ratio of STC-adjusted versus unadjusted HRs. Consequently, AIC and BIC statistics are not available for the adjusted analyses of lifileucel PFS. Comparisons of the model-predicted versus (adjusted) observed PFS for the adjusted lifileucel MCMs are presented in Figure 17. The company's STC-adjusted survival approach does not directly yield alternative cure fractions as new MCMs have not been fitted; however, the implied cure fractions for these adjusted

models can be estimated by removing general population mortality risks from the uplifted MCMs. The implied cure fractions from the lifileucel MCMs for PFS after STC adjustment are shown in Table 32. Hazard plots are not presented in the CS[1] for the adjusted lifileucel model.

Figure 17: Kaplan-Meier plots and fitted MCMs, PFS, lifileucel-infused population, Study C-144-01, STC-adjusted (generated using the company's model)

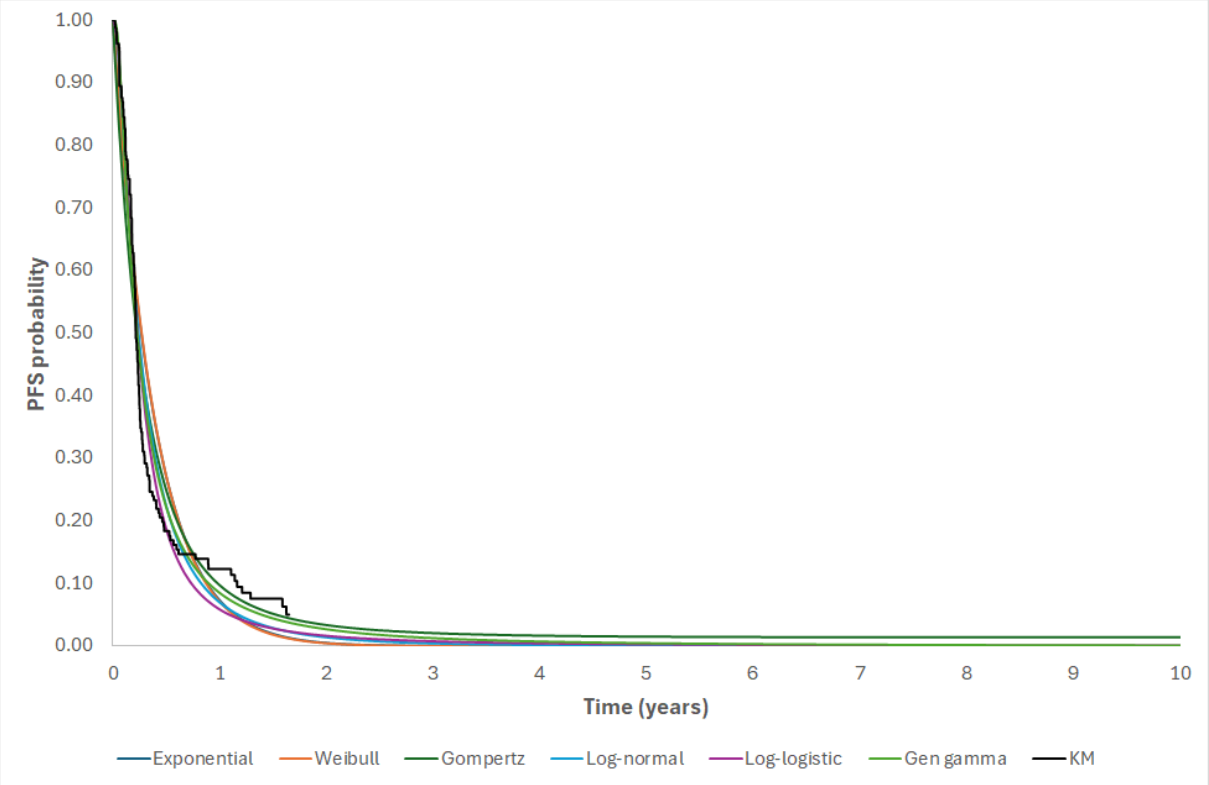
PFS - progression-free survival; KM - Kaplan-Meier

The PFS outcomes adjusted to the characteristics of the da Silva *et al.*[52] ipilimumab population are more optimistic compared with the unadjusted PFS models (see Figure 17 and Figure 15, respectively). The implied cure fractions across the STC-adjusted lifileucel MCMs for PFS range from [redacted] to [redacted]. The CS[1] states that the log-normal MCM was used as the base case model for adjusted lifileucel PFS to reflect the unadjusted analysis.

Ipilimumab PFS

The CS[1] states that only standard parametric survival models were fitted to the observed PFS data for ipilimumab because of the short duration of a plateau for PFS and insufficient follow-up in da Silva *et al.*[52] The fitted PFS models therefore do not allow for the possibility of cure in any patients. AIC and BIC statistics for the survival models fitted to the ipilimumab PFS data are shown in Table 31. Comparisons of model-predicted versus observed PFS for the ipilimumab standard parametric models are presented in Figure 18. Comparisons of observed and model-predicted hazards for the ipilimumab group are not presented in the CS.[1]

Figure 18: Kaplan-Meier plots and fitted standard parametric models, PFS, ipilimumab, da Silva *et al.* (generated using the company's model)



PFS - progression-free survival; KM - Kaplan-Meier

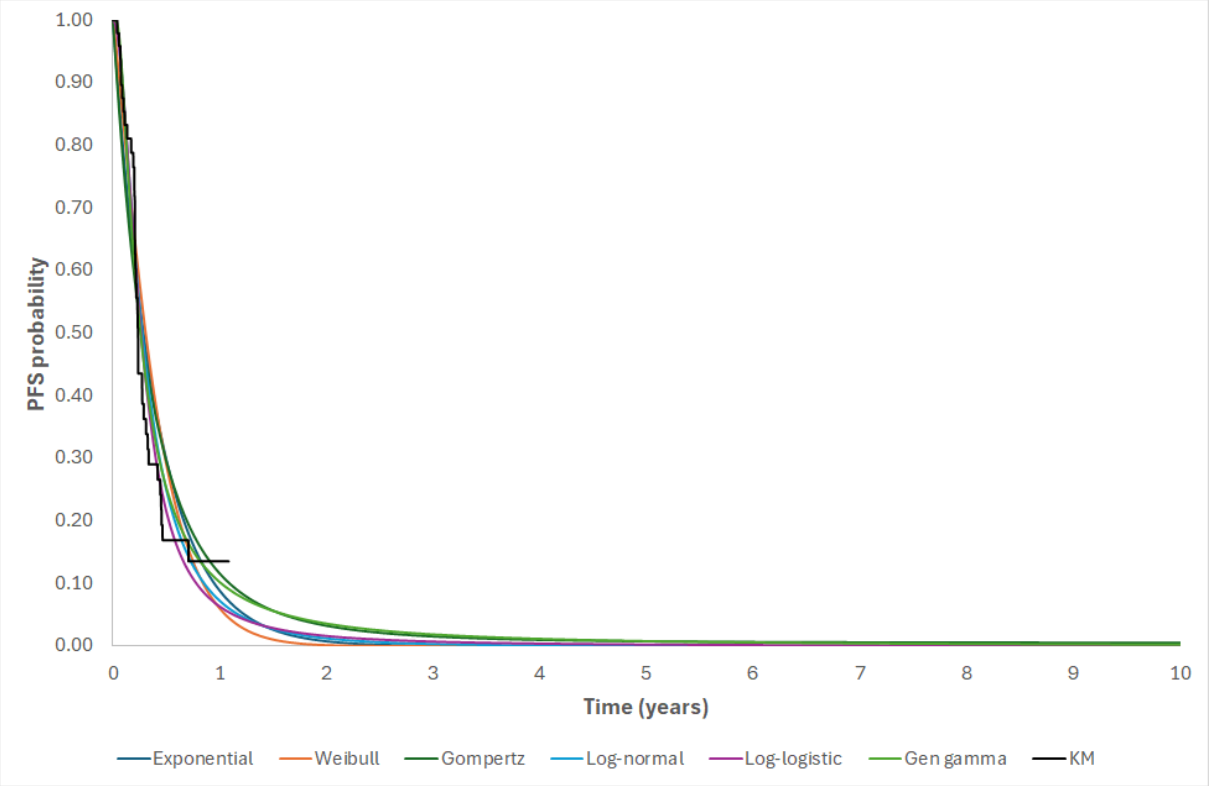
Amongst the standard parametric models fitted to the PFS data for ipilimumab, the log-logistic distribution is the best-fitting model based on both the AIC and BIC. None of the fitted models provide a good visual representation of the observed PFS data. Three of the fitted models predict a PFS at 3 years which is 1% or greater: these are the Gompertz (2%), log-logistic (1%) and generalised gamma (1%). All models except for the Gompertz distribution predict a PFS probability of approximately zero at 5 years. The CS[1] states that the log-logistic distribution was selected for inclusion in the base case model for ipilimumab PFS following feedback from the one-to-one meetings with clinical experts.[70] However the EAG notes that the minutes of these meetings indicate that one clinician believed that none of the distributions were suitable because they all indicate a long-term survival probability of 0–1% (which was lower than clinical expectations), whereas the other clinician expressed a preference for the log-logistic distribution due to *"high upfront attrition."*

Chemotherapy PFS

The CS[1] states that only standard parametric survival models were fitted to the observed PFS data for chemotherapy because of the short duration of a plateau for PFS, insufficient follow-up and the absence of a plateau in the observed OS in Mangin *et al.*,[30] and because the mechanism of action for chemotherapy is a hindrance to cure. AIC and BIC statistics for the survival models fitted to the chemotherapy PFS data are shown in Table 31. Comparisons of model-predicted versus observed PFS

for the chemotherapy group are presented in Figure 19. Comparisons of observed and model-predicted hazards for the chemotherapy group are not presented in the CS.[1]

Figure 19: Kaplan-Meier plots and fitted standard parametric models, PFS, chemotherapy, Mangin *et al.* (generated using the company's model)



PFS - progression-free survival; KM - Kaplan-Meier

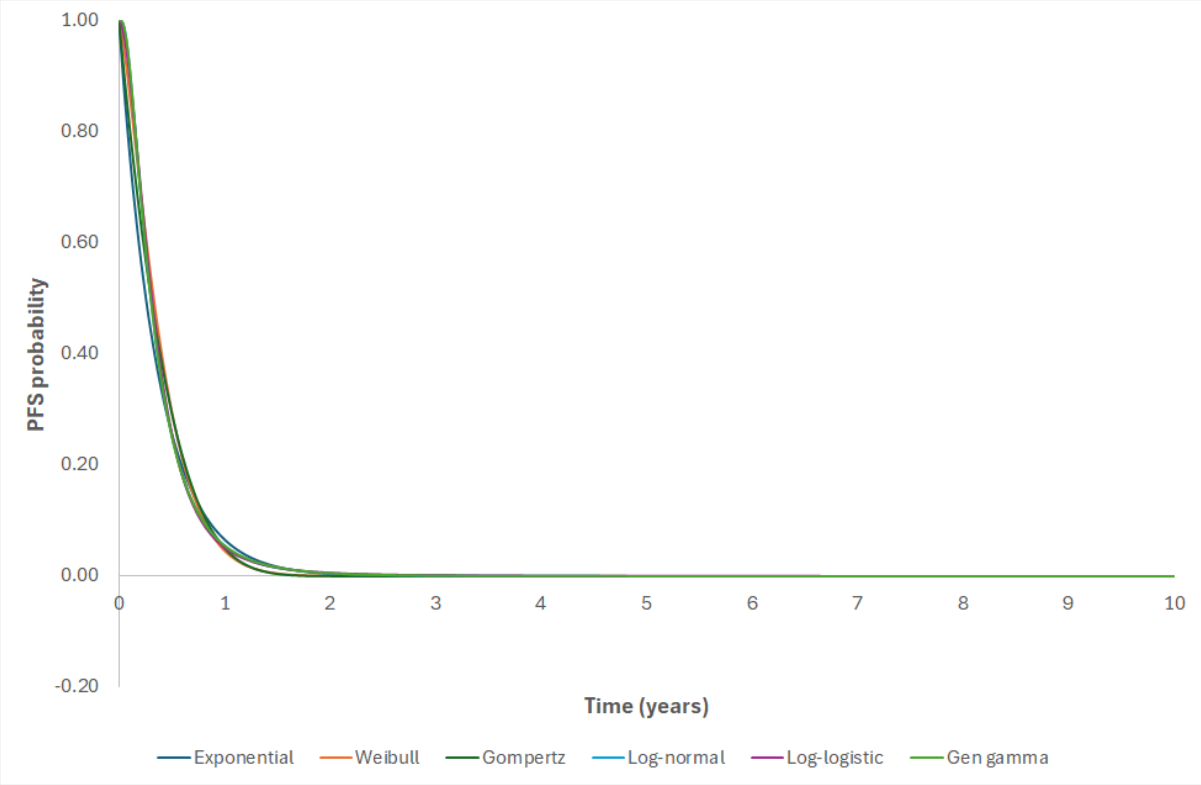
Amongst the fitted chemotherapy survival models, the log-logistic distribution is the best-fitting model according to both the AIC and BIC; the log-normal distribution has similar AIC and BIC values, and the generalised gamma distribution has a similar AIC value. None of the models provide a particularly good visual representation of the data, although the visual fit of the log-logistic, log-normal and generalised gamma distributions appears to be slightly better than the other distributions. The CS[1] states that the log-logistic distribution was selected for inclusion in the base case model because the clinicians who attended the company's advisory board meeting confirmed that all of the fitted models appeared plausible, and they agreed that it was reasonable to select the best-fitting model based on AIC and BIC statistics.

BSC PFS

No data were available for BSC; hence, BSC outcomes were modelled by applying an HR of 2.0 to the selected parametric survival model for the chemotherapy group. This assumed HR was based on a structured elicitation exercise undertaken at the company's advisory board meeting which indicated that outcomes for BSC would be *"50% worse"* than those for chemotherapy.[26] Model-predicted PFS for

BSC is presented in Figure 20. The CS[1] states that the log-logistic distribution was selected for inclusion in the company's base case model for BSC PFS to reflect the choice made for PFS in the chemotherapy group.

Figure 20: Kaplan-Meier plots and fitted standard parametric models, PFS, BSC, assumed (generated using the company's model)



PFS - progression-free survival

5.2.4.2.3 Overall survival (OS)

OS for patients receiving the lifileucel infusion was estimated using IPD from Study C-144-01;[28] the survival analysis was conducted on the pooled data of Cohorts 2 and 4 from the PDAwCS efficacy set. As with the PFS analysis, OS for patients receiving ipilimumab and chemotherapy was estimated from survival data from da Silva *et al.*[52] and Mangin *et al.*,[30] respectively. Pseudo-IPD from these studies were generated using the algorithm reported by Guyot *et al.*[92] No data were available on OS for patients receiving BSC; instead, OS for BSC was obtained by applying an HR of 2.0 to the fitted survival models for chemotherapy.

AIC and BIC statistics for the parametric survival models fitted to the OS data for lifileucel, ipilimumab and chemotherapy are shown in Table 33.

Table 33: AIC and BIC values for models of OS

Model	**Lifileucel (unadjusted)**		**Ipilimumab**		**Chemotherapy**		**BSC**	
Mixture cure-models	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential MCM*	[redacted]	[redacted]	MCMs were not considered for ipilimumab, chemotherapy or BSC.					
Weibull MCM								
Gompertz MCM								
Log-normal MCM								
Log-logistic MCM								
Generalised gamma MCM								
Standard models	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	Standard models are not considered in the company's base case. AIC and BIC values are available from the CS.[1]		750.66	753.75	237.22	239.14	Not applicable for BSC.	
Weibull			750.59	756.77	235.19	239.01		
Gompertz			752.63	758.81	237.62	241.44		
Log-normal†			**739.47**	**745.64**	**232.56**	**236.39**		
Log-logistic			742.24	748.41	233.56	237.39		
Generalised gamma			741.12	750.39	234.56	240.29		

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; OS - overall survival; MCM - mixture-cure model; BSC - best supportive care; CS - company's submission.
The AIC / BIC values of the best-fitting model are highlighted in bold.
** Model selected for OS for lifileucel in company's base case.*
† Model selected for OS for all comparators in company's base case.

Lifileucel OS, unadjusted

Similar to PFS, the CS[1] states that a plateau in the observed OS data for lifileucel supports the use of MCMs because these models are able to effectively capture the change in the hazard function. The CS states that the use of MCMs for lifileucel OS was supported by UK clinicians at an advisory board meeting who shared experiences of *"long term survivors treated with lifileucel"* returning to *"normal function"* and *"full normalcy."*[26] AIC and BIC statistics for the MCMs fitted to the lifileucel OS data are shown in Table 33. Comparisons of model-predicted versus observed OS for the lifileucel MCMs are presented in Figure 21. Estimated cure fractions from the lifileucel MCMs for OS are presented in Table 34. A comparison of observed and model-predicted hazards for OS for the lifileucel exponential MCM is presented in Figure 22.

Figure 21: Kaplan-Meier plots and fitted MCMs, OS, lifileucel-infused population, Study C-144-01, unadjusted (generated using the company's model)

OS - overall survival; KM - Kaplan-Meier

Table 34: Estimated cure fractions for lifileucel for OS

Mixture cure-models	Cure fraction estimated using MCM	Implied cure fraction after STC adjustment†
Exponential MCM*		
Weibull MCM		
Gompertz MCM		
Log-normal MCM		
Log-logistic MCM		
Generalised gamma MCM		

OS - overall survival; STC - simulated treatment comparison; MCM - mixture-cure model
** Model selected for OS for lifileucel in company's base case*
† Estimated by including the STC-adjusted hazard ratio and removing general population mortality risks from the MCM

Figure 22: Comparison of the observed and predicted OS hazards for Study C-144-01 and log-logistic MCM (reproduced from CS, Figure 26)

MCM - mixture cure model; OS - overall survival
Note: General population OS hazards represent US life tables

Amongst the lifileucel MCMs, the exponential MCM is the best-fitting model based on both the AIC and BIC. The AIC statistics for all models are generally similar whereas the BIC statistic for the exponential MCM is noticeably lower than that of the other MCMs. All models provide a similar visual representation of the observed OS data. The MCMs for lifileucel OS indicate cure fractions ranging from [redacted] to [redacted]. Among the three best-fitting models, the exponential MCM resulted in the highest cure fraction ([redacted]) compared with the log-logistic and log-normal MCMs ([redacted] and [redacted], respectively). The CS[1] states that the exponential MCM was selected for inclusion in the base case model following feedback from one-to-one meetings with clinical experts. The minutes of these meetings indicate that one clinician believed that *"all curves were consistent and plausible"* whilst the other expert believed that *"OS of [redacted] was too high and that [redacted] would be more plausible."* The EAG notes the latter clinician expressed that *"in this line of treatment there is little difference between PFS and OS in terms of cure fraction"*, yet the company's base case model selections result in a [redacted] difference between the cure fractions for PFS and OS. One clinical expert suggested selecting the same parametric model form for OS as that selected for PFS, whereas the other expert highlighted the need to justify any selection on statistical grounds.

Lifileucel OS, adjusted

As with PFS, the unadjusted MCMs for OS were uplifted using the ratio of STC-adjusted and unadjusted HRs. Consequently, AIC and BIC statistics are not available for the adjusted analyses of OS for lifileucel. Comparisons of model-predicted versus (adjusted) observed OS for the adjusted lifileucel MCMs are presented in Figure 21. Estimated cure fractions from the lifileucel MCMs for OS after STC adjustment were presented previously in Table 34. Hazard plots are not presented in the CS[1] for the adjusted lifileucel model.

Figure 23: Kaplan-Meier plots and fitted MCMs, OS, lifileucel-infused population, Study C-144-01, STC-adjusted (generated using the company's model)

OS - overall survival; KM - Kaplan-Meier

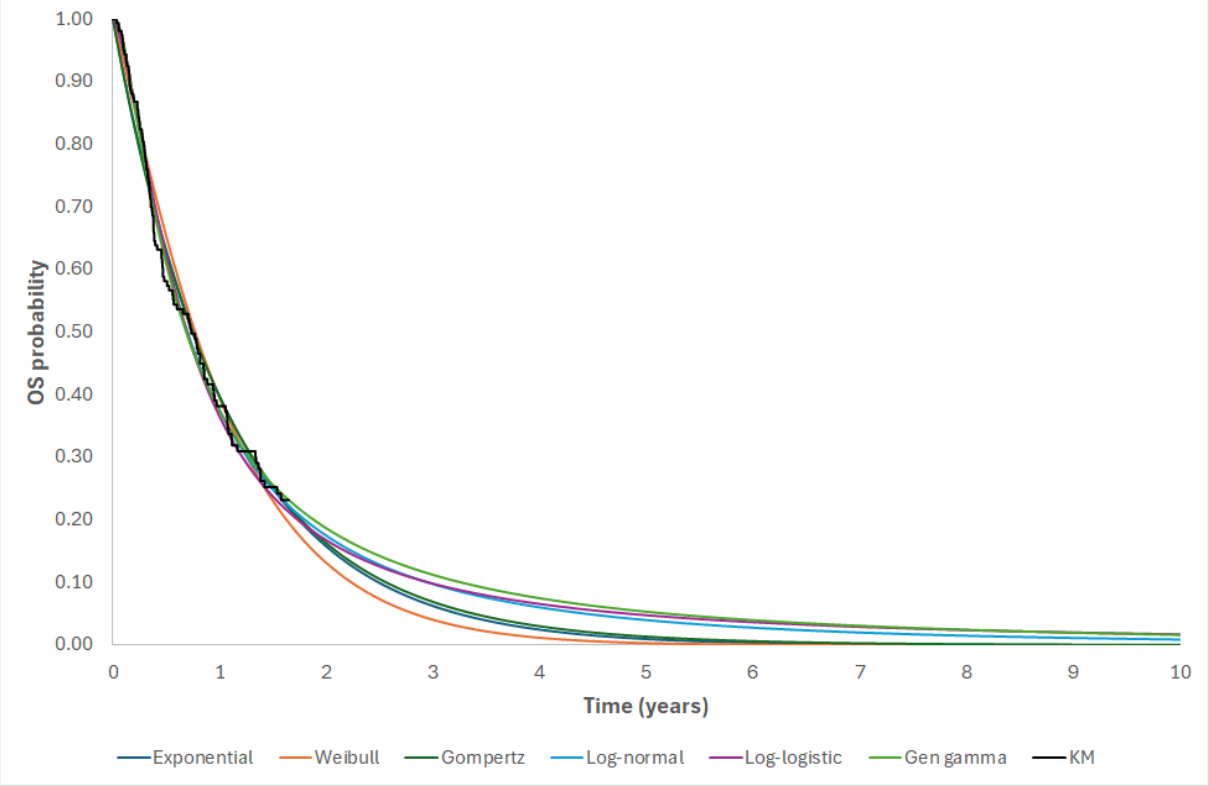
The OS outcomes adjusted to the characteristics of the da Silva *et al.*[52] ipilimumab population are more optimistic compared with the unadjusted OS models (see Figure 23 and Figure 21, respectively). The implied cure fractions across the STC-adjusted MCMs for OS range from [redacted] to [redacted]. The CS[1] states that the exponential MCM was used as the base case model for adjusted lifileucel OS to reflect the unadjusted analysis.

Ipilimumab OS

Similar to PFS, the CS[1] states that only standard parametric survival models were fitted to the observed OS data for ipilimumab due to insufficient follow-up in da Silva *et al.*[52] However, clinicians who attended the company's advisory board meeting estimated the long-term survival (≥5 years) of

ipilimumab-treated patients to be between 0% and 5%. The company accounted for this in their base case model by assuming that ipilimumab-treated patients who remain progression-free at 3 years achieve long-term survival (equivalent to cure). This is applied in the model by assuming that the proportion of ipilimumab-treated patients who are alive and progression-free at this time point are subsequently subject to general population risks, whereas those who have progressed at this time point have mortality risks based on the OS model fitted to the observed OS data from da Silva *et al.* The EAG notes that the ipilimumab PFS model does not include a similar assumption and "cured" ipilimumab patients continue to experience disease progression risks beyond 3 years (i.e., they are cured for OS but not PFS). AIC and BIC statistics for the survival models fitted to the ipilimumab OS data are shown in Table 33. Comparisons of model-predicted versus observed OS for the ipilimumab standard parametric models are presented in Figure 24. Comparisons of observed and model-predicted hazards for the ipilimumab group are not presented in the CS.[1]

Figure 24: Kaplan-Meier plots and fitted standard parametric models, OS, ipilimumab, da Silva *et al.*, (generated using the company's model)



OS - overall survival; KM - Kaplan-Meier

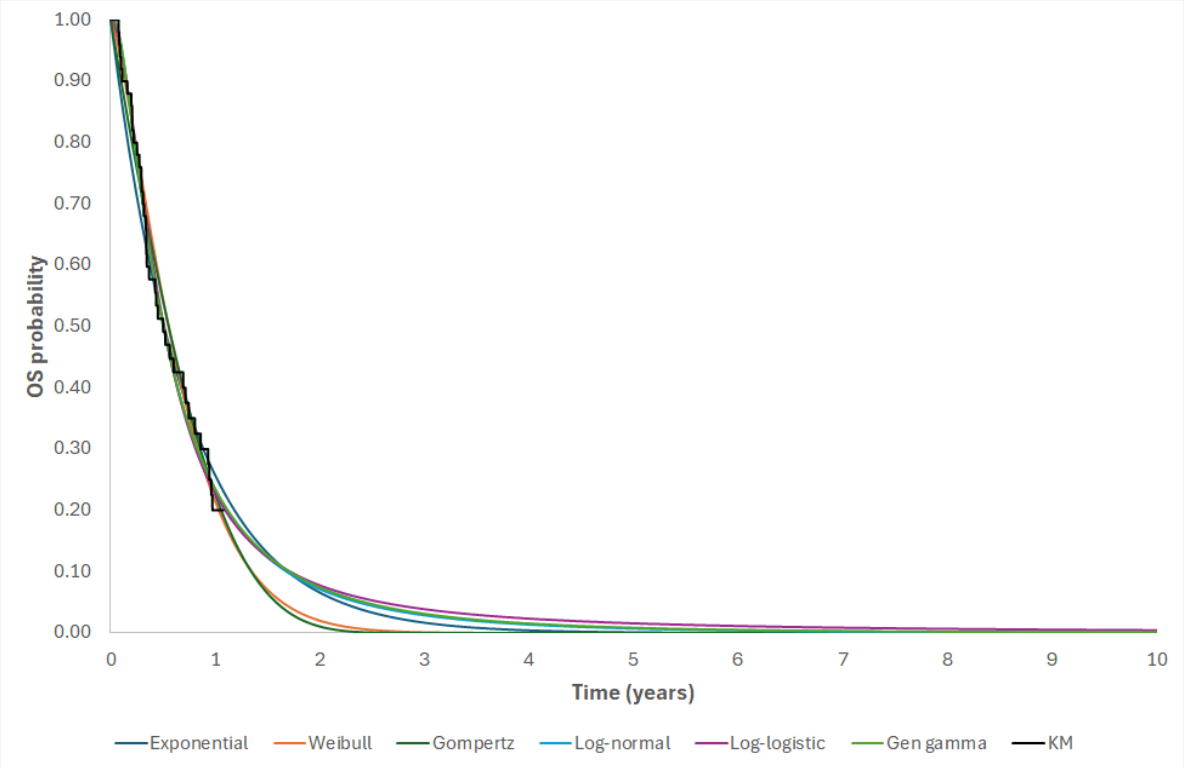
Amongst the standard parametric models fitted to the PFS data for ipilimumab, the log-normal distribution is the best-fitting model based on both the AIC and BIC; the log-logistic model has a similar AIC and BIC and the generalised gamma model has a similar AIC. All models provide a similar visual fit to the observed data; however, the exponential, Weibull and Gompertz distributions predict a sharper decline in OS beyond the observed period compared to the log-normal, log-logistic and generalised

gamma distributions. All distributions predict a non-zero probability of OS at 3 years ranging from 4% to 11%, with the log-normal, log-logistic and generalised gamma distributions each predicting an OS probability of at least 10% at this timepoint. OS predictions at 5 years range from 0% to 5%, with the log-normal distribution predicting 4% and the log-logistic and generalised gamma distributions predicting 5%. The CS[1] states that the log-normal distribution was selected for inclusion in the base case for ipilimumab OS following feedback from the one-to-one meetings with clinical experts.[70] The minutes of these meetings indicate that both clinical experts noted patients who remained alive at 3 years could be considered long-term survivors. The experts commented that if patients progressed, they would not survive to three years, noting that 10% survival would be too high. The EAG notes however that the fitted OS models relate to all patients treated with ipilimumab, rather than those patients who have progressed during or after treatment with ipilimumab. One clinician expressed a preference for the log-logistic distribution due to *"high upfront attrition."*

Chemotherapy OS

The CS[1] states that only standard parametric survival models were fitted to the observed OS for chemotherapy because of the absence of a plateau in Mangin *et al.*[30] AIC and BIC statistics for the survival models fitted to the chemotherapy OS data are shown in Table 33. Comparisons of model-predicted versus observed OS for the chemotherapy group are presented in Figure 25. Comparisons of observed and model-predicted hazards for the chemotherapy group are not presented in the CS.

Figure 25: Kaplan-Meier plots and fitted standard parametric models, OS, chemotherapy, Mangin *et al.* (generated using the company's model)



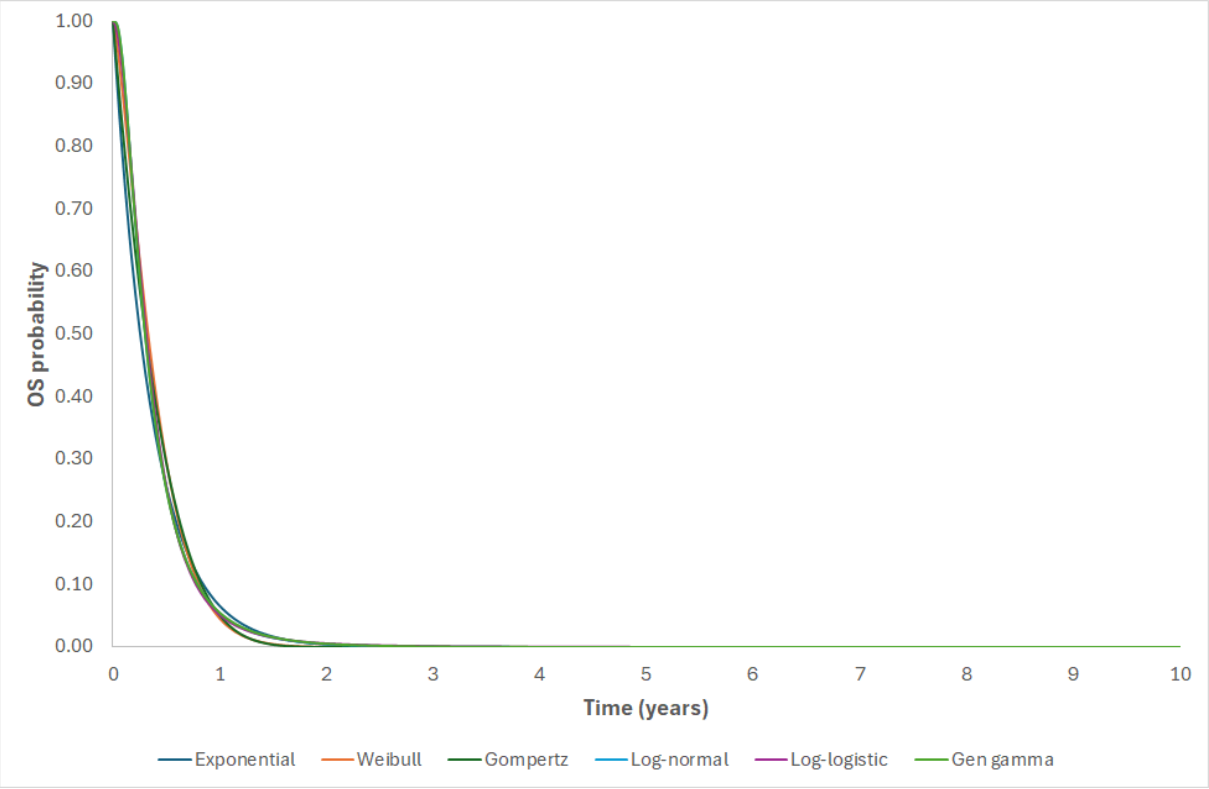
OS - overall survival; KM - Kaplan-Meier

Amongst the chemotherapy survival models, the log-normal distribution is the best-fitting model according to both the AIC and BIC. The AIC and BIC values for the Weibull, log-logistic and generalised gamma distributions are similar to those for the log-normal model. All models provide a similar visual fit to the observed data; the key difference is that the Weibull and Gompertz distributions predict a sharper decline in OS beyond the observed period. Four distributions predict OS probabilities at 3 years which are ≥1%: the exponential (2%), log-logistic (4%), log-normal (3%) and generalised gamma (3%) distributions. Three distributions predict an OS probability of ≥1% at 5 years: the log-logistic (2%), log-normal (1%) and generalised gamma (1%) distributions. The CS[1] states that the log-normal distribution was selected because the clinicians who attended the company's advisory board meeting[70] confirmed that all of the fitted models appeared plausible and they agreed that it was reasonable to select the best-fitting model based on AIC and BIC statistics.

BSC OS

No data were available for BSC; hence, BSC outcomes were modelled by applying an HR of 2.0 to the selected OS model for the chemotherapy group, based on a structured elicitation exercise undertaken at the company's advisory board meeting. Model-predicted OS for BSC is presented in Figure 26. The CS[1] states that the log-normal distribution was used in the base case model for BSC OS to reflect the choice made for the OS of chemotherapy.

Figure 26: Kaplan-Meier plots and fitted standard parametric models, OS, BSC, assumed (generated using the company's model)



OS - overall survival

5.2.4.2.4 Summary of company base case model predictions

Table 35 summarises the parametric survival distributions selected for inclusion in the company's base case model. The company's base case model includes two scenarios: (i) an STC-adjusted comparison of lifileucel versus ipilimumab; and (ii) a naïve comparison of lifileucel versus chemotherapy and BSC. These comparisons are shown graphically in Figure 27 and Figure 28, respectively. These plots are based on the final economic model trace, including general population mortality risks.

Table 35: Summary of distributions selected for inclusion in the company's base case model

Outcome	Treatment group	Base case model selection	Cure fraction
PFS	Unadjusted lifileucel	Log-normal MCM	[redacted]
	STC-adjusted lifileucel	Log-normal MCM	
	Ipilimumab	Log-logistic	N/a
	Chemotherapy	Log-logistic	N/a
	BSC		N/a
OS	Unadjusted lifileucel	Exponential MCM	[redacted]
	STC-adjusted lifileucel		
	Ipilimumab	Log-normal	N/a
	Chemotherapy	Log-normal	N/a
	BSC		N/a

BSC - best supportive care; MCM - mixture-cure model; OS - overall survival; PFS - progression-free survival; STC - simulated treatment comparison; N/a - not applicable

Figure 27: Model predictions of PFS and OS for lifileucel versus ipilimumab, includes STC-adjustment (generated using the company's model)

[redacted]

PFS - progression-free survival; OS - overall survival
Note: This plot has been generated using the final model trace – it includes probability that patients do not receive the lifileucel infusion and incorporates general population mortality constraints

Figure 28: Model predictions of PFS and OS for lifileucel versus chemotherapy and BSC, naïve ITC (generated using the company's model)

PFS - progression-free survival; OS - overall survival; BSC - best supportive care
Note: This plot has been generated using the final model trace – it includes probability that patients do not receive the lifileucel infusion and incorporates general population mortality constraints

5.2.4.3 Frequency of adverse events

The company's model includes Grade ≥3 AEs occurring in ≥5% of patients in any of the treatment groups. The AE frequencies for the lifileucel treatment group are based on TEAE incidence rates reported for the SAS population in Study C-144-01[28] (pooled Cohorts 2 and 4), and include AEs which started between the lifileucel infusion up to 30 days post-lifileucel infusion. The frequencies for ipilimumab and chemotherapy are based on da Silva *et al.*[52] and Mangin *et al.*,[30] respectively. The model assumes that patients receiving BSC do not experience any AEs. Population-adjustment methods were not applied to the AE data. Table 36 summarises the AE frequencies applied to each treatment group in the company's base case model.

Table 36: Frequency of Grade ≥3 AEs in the model

AE	Frequency			
	Lifileucel	Ipilimumab‡	Chemotherapy	BSC
Thrombocytopenia	[redacted]	1.00%	1.76%	0.00%
Anaemia	[redacted]	1.00%	2.64%	0.00%
Neutropenia	[redacted]	0.00%	1.32%	0.00%
Lymphopenia	[redacted]	0.00%	0.00%	0.00%
Leukopenia	[redacted]	0.00%	0.00%	0.00%
Febrile neutropenia	[redacted]	0.00%	5.00%	0.00%
Hypophosphatemia	[redacted]	0.00%	0.00%	0.00%
Hypoxia	[redacted]	0.00%	0.00%	0.00%
Hypotension	[redacted]	0.00%	0.00%	0.00%
Pyrexia	[redacted]	0.00%	5.00%	0.00%
Hypertension	[redacted]	0.00%	5.00%	0.00%
Rash maculo-papular	[redacted]	1.00%	5.00%	0.00%
Chills	[redacted]	0.00%	5.00%	0.00%
Diarrhoea or colitis	[redacted]	20.00%	0.00%	0.00%
Increased ALT/AST	[redacted]	9.00%	0.00%	0.00%
Hypophysitis	[redacted]	5.00%	0.00%	0.00%

AE - adverse event; BSC - best supportive care; ALT - alanine aminotransferase; AST - aspartate aminotransferase
‡ The EAG notes that the AE frequencies used in the company's model are rounded down to integer values. In addition, da Silva et al. includes anaemia and thrombocytopenia as one category, and the company included both as separate events, assuming the same incidence for both.

5.2.4.4 HRQoL

The model includes HRQoL parameters related to: (i) health state utility values; (ii) a short-term QALY loss associated with the lifileucel administration (lifileucel treatment group only); and (iii) short-term QALY losses associated with Grade ≥3 TEAEs. Health state utility values are adjusted for increasing age. Table 37 summarises the HRQoL data included in the company's base case model; the derivation of these parameters is described in further detail in the subsequent sections.

Table 37: HRQoL parameters for each comparator used in the model

HRQoL parameter	Treatment group			
	Lifileucel	Ipilimumab	Chemotherapy	BSC
Health state mean utility - PF state	0.77†			
Health state mean utility - PD state	0.67			
Disutility related to lifileucel administration	0.09	0.00		
Disutility related to AEs	[redacted]	0.02	0.03	0.00

AE - adverse event; PD - progressed disease; PF - progression-free; QALY - quality-adjusted life year
† For the lifileucel and ipilimumab treatment groups, patients who remain in the PF state after 3 years are assumed to incur the same utility as the age- and sex-matched general population.

5.2.4.4.1 Health state utility values

Study C-144-01[28] included HRQoL data collection using the European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire (EORTC QLQ-C30). The questionnaire was

administered at variable points according to patients' visit schedules (e.g., screening, pre-infusion, follow-up visits) and at unscheduled assessments, until disease progression or the start of new anticancer therapy (clarification response,[27] question B11). The company mapped the QLQ-C30 data (DCO 24th February 2022) to the EQ-5D-3L using three different mapping models (Versteegh *et al.*,[93] Kim *et al.*[94] and Wojciechowski *et al.*);[95] these mapping analyses are reported in CS,[1] Section 3.4.2 and CS Appendix N.[13] The company then summarised the results at baseline, Week 12, Month 6, Month 12, and Month 24 for the FAS Pooled Cohorts 2 and 4 to estimate health state utility values. The company's clarification response (question B11) states that they considered using imputation methods to handle missing data, but that these were considered inappropriate due to: *"(1) the exploratory nature of the QLQ-C30 data collection in the study, (2) the relatively small sample size available, and (3) the desire to minimize additional uncertainty and bias that would be introduced through imputation methods especially if missingness mechanism is not completely at random."* Instead, any missing responses were excluded. The company also clarified that they did not fit any statistical models to the mapped data and that only descriptive statistics were calculated. The company justified the use of an earlier DCO compared with the clinical outcomes DCO (30th June 2023) on the basis that a sufficient volume of data were available and HRQoL was only an exploratory outcome in Study C-144-01 (clarification response, question B11).

Section 3.4.2 of the CS[1] states that in Study C-144-01,[28] HRQoL data were not systematically collected post-event and the data were not sufficiently robust to calculate changes in utility over time. In response to clarification question B11,[27] the company also stated that whilst the mean/median utility scores from the Kim and Wojciechowski mapping models were consistent with values from the published literature for similar melanoma populations, the data presented several limitations, namely:

(1) Data sparsity: *"[redacted] of patients had only one or two QLQ-C30 assessments available and the average time between visits with assessments was [redacted] days limiting the ability to reliably characterize changes in HRQoL over time or by health states"*;
(2) Exploratory data collection: HRQoL data was only an exploratory outcome of Study C-144-01;
(3) Risk of bias from missing data: missing data was not random in the study *"which could affect the statistical reliability of mapped utility estimates"*;
(4) Uncertainty in the mapping results: the mapping models were based on different populations (not UK population);

The company used these justifications as the basis for using health state utility values from published estimates rather than Study C-144-01.[28] This issue is discussed in further detail in Section 5.3.5.

The company undertook an initial SLR in August 2024 and an updated SLR in January 2025 to identify published HRQoL studies which are relevant to the decision problem. The SLR identified the following publications which report HRQoL estimates for patients receiving 1L or 2L treatment for advanced

melanoma: three published studies,[61, 62, 96] 12 NICE TAs (including one TA which did not report utility values and which was therefore excluded),[15-22, 65-67] and one NICE guideline.[14] However, the company used only a selected set of these sources to inform the health state utility values in the model: 2 published studies[61, 62] and 10 TAs.[15-22, 65-67] The reasons for excluding the other publications are unclear. The company estimated health state utility values for the progression-free (PF) and progressed disease (PD) states based on unweighted means of the utility values reported in the 12 selected sources. A summary of the external sources retrieved by the company's SLR and used to derive the model health utilities is presented in Table 38.

Table 38: Summary of utility estimates identified from company's SLR (adapted from CS, Appendix F, Table 26 and Table 27)

Reference	Study design	Population	Line of therapy	HRQoL instrument	Health state utilities reported	Health state utilities used in the company's model
Published studies						
ten Ham *et al.* (2024)[62]	Prospective cost-utility analysis of TIL-NKI/CCIT versus ipilimumab, based on phase III RCT (NCT02278887).	Unresectable stage IIIC-IV melanoma after failure of 1L or 2L treatment	2L or 3L	EQ-5D-3L (Dutch and Danish tariffs)	Stable disease (baseline)[a]: • Ipilimumab: 0.838 • TIL-NKI/CCIT: 0.874 Progressive disease: • Ipilimumab (rechallenge): 0.764 • Ipilimumab/nivolumab combination therapy: 0.695 • BRAF/MEK inhibitor: 0.844 • Pembrolizumab: 0.707 • Temozolomide: 0.730 • Dacarbazine: 0.791 • No treatment after TIL-NKI/CCIT: 0.832 • No treatment after ipilimumab: 0.764	Progression free: 0.77[†] Progressive disease: not used
Retel *et al.* (2018)[61]	Early cost-effectiveness model based on a hypothetical cohort of TIL versus ipilimumab as second line treatment	Previously treated metastatic melanoma (stage IV)	2L	Standard gamble (from Beusterien *et al.*[97]	Progression free: 0.850 Progressive disease: 0.590	Progression free: 0.850 Progressive disease: 0.590
Schadendorf *et al.* (2024)[96]	Analysis of 7.5 year follow of HRQoL data from patients receiving nivolumab, nivolumab plus ipilimumab or ipilimumab monotherapy in the randomised double-blind RCT (Checkmate-067 study).	Adult patients with untreated unresectable or metastatic melanoma.	1L	EORTC QLQ-C30 EQ-5D-3L and VAS (from Checkmate-067 study)	Baseline PRO scores (ITT with baseline) – N, Mean (SD): • EORTC QLQ-C30[*]: • GHS/QoL: N = 860, mean = 72.0 (21.38) • Physical functioning: N = 861, mean = 85.7 (19.00) • Role functioning: N = 861, mean = 81.8 (26.26) • Emotional functioning: N = 861, mean = 76.9 (18.55) • Cognitive functioning: N = 861, mean = 90.2 (15.92)	Utilities not used by the company in the model

Reference	Study design	Population	Line of therapy	HRQoL instrument	Health state utilities reported	Health state utilities used in the company's model
					• Social functioning: N = 860, mean = 82.6 (23.27) EQ-5D-3L: • Utility index: N = 716, mean = 0.78 (0.24)§ • Visual analogue scale: N = 716, mean = 75.1 (19.40)	
Previous NICE TAs or guidelines						
TA 268[65]	Cost-utility analysis of ipilimumab as 2L or 3L treatment versus BSC	Patients with stage III or stage IV unresectable or metastatic melanoma who have received prior treatment	2L	EORTC-QLQ-C30 (from MDX010-20 trial) mapped to EQ-5D	Progression-free: 0.80 Progressive disease: 0.76	Progression-free: 0.80 Progressive disease: 0.76
TA269[15]	Cost-utility analysis of vemurafenib versus dacarbazine as a 1L or 2L treatment	BRAF V600 mutation positive unresectable or metastatic melanoma.	1L or 2L (not fully clear)	Standard gamble (from Beusterien *et al.*[97] and Nafees *et al.*)[98]	Progression free: • Vemurafenib: 0.806 • Dacarbazine: 0.767 Progressive disease: 0.59	Progression free: 0.79‡ Progressive disease: 0.59
TA319[16]	Cost-utility analysis of ipilimumab versus BSC, dacarbazine monotherapy and vemurafenib monotherapy	Patients with untreated unresectable or metastatic melanoma	1L	EORTC QLQ-C30 (from CA184-024 Trial)	Progression-free: • Placebo + DTIC: 0.85 • Ipilimumab + DTIC: 0.84 Progressive disease: • Placebo +DTIC: 0.84 • Ipilimumab + DTIC: 0.83	Progression free: 0.83† Progressive disease: not used
TA321[17]	Cost-utility analysis of dabrafenib versus vemurafenib or dacarbazine	Patients with untreated unresectable or metastatic BRAF V600 mutation positive melanoma	1L[b]	EQ-5D (from BREAK-3 trial) (EAG report suggests VAS was used)	Progression free: • Dabrafenib: 0.77 • Vemurafenib: 0.77 • Dacarbazine: 0.75 Progressive disease: • Dabrafenib: 0.68 • Vemurafenib: 0.68	Progression free: 0.76‡ Progressive disease: 0.68‡

Reference	Study design	Population	Line of therapy	HRQoL instrument	Health state utilities reported	Health state utilities used in the company's model
					• Dacarbazine: 0.68	
TA357[18]	Cost-utility analysis of pembrolizumab versus dacarbazine monotherapy, paclitaxel monotherapy, carboplatin monotherapy, temozolomide monotherapy and combination paclitaxel + carboplatin	Patients with unresectable or metastatic melanoma following progression on ipilimumab	2L	EQ-5D (from KEYNOTE-002 trial)	Progression free: • MK3475 2mg: 0.75 • Chemotherapy: 0.73 • MK2375 2mg + Chemotherapy: 0.74 Progressive disease: • MK3475 2mg: 0.69 • Chemotherapy: 0.68 • MK2375 2mg + Chemotherapy: 0.68	Progression free: 0.74‡ Progressive disease: 0.69‡
TA366[19]	Cost-utility analysis of pembrolizumab versus ipilimumab monotherapy, vemurafenib monotherapy, dacarbazine monotherapy or dabrafenib monotherapy	Patients with unresectable or metastatic melanoma who are ipilimumab naïve	1L	EQ-5D-3L (from KEYNOTE-006 trial)	Progression free: • MK3475 10mg: 0.81 • Ipilimumab: 0.77 • Pooled: 0.80 Progressive disease: • MK3475 10mg: 0.71 • Ipilimumab: 0.68 • Pooled: 0.70	Progression free: 0.70† Progressive disease: not used
TA384[66]	Cost-utility analysis of nivolumab monotherapy versus ipilimumab monotherapy, dabrafenib monotherapy, vemurafenib monotherapy or dacarbazine monotherapy	Patients with unresectable or advanced melanoma who are treatment-naive	1L	EQ-5D-3L (from Checkmate 066 trial)	Progression free with time to death: • 30 days or less: 0.7795 • More than 30 days: 0.8014 Progressive disease with time to death: • 30 days or less: 0.7054 • More than 30 days: 0.7277	Progression free: 0.72† Progressive disease: not used
TA396[20]	Cost-utility analysis of trametinib in combination with dabrafenib versus dabrafenib monotherapy or vemurafenib monotherapy	Adults with unresectable or metastatic melanoma in adults with a BRAF V600 mutation	1L	EQ-5D-3L (from COMBI-d and COMBI-v trials)	Progression free: • Trametinib + dabrafenib: 0.837 • Vemurafenib: 0.746 • Dabrafenib: 0.789 Progressive disease: 0.697	Progression free: 0.791‡ Progressive disease: 0.697‡
TA400[21]	Cost-utility analysis of nivolumab in combination with ipilimumab versus ipilimumab monotherapy, pembrolizumab	Adults with untreated unresectable or metastatic melanoma.	1L	EQ-5D-3L (from Checkmate 067 trial)	Progression-free: 0.7954 Progressive disease: 0.7625	Progression free: 0.76† Progressive disease: not used

Reference	Study design	Population	Line of therapy	HRQoL instrument	Health state utilities reported	Health state utilities used in the company's model
	monotherapy or dabrafenib and vemurafenib (for BRAF V600 mutation-positive people)					
TA410[67]	Cost-utility analysis of talimogene laherparepvec versus ipilimumab monotherapy, vemurafenib (for people with BRAF V600 mutation-positive melanoma) or dabrafenib (for people with BRAF V600 mutation positive melanoma) where there is no restriction on treatment line.	Adults with stage IIIB-IV unresectable melanoma where there is no bone, brain, lung or other visceral disease.	1L	EQ-5D (from TA321 - BREAK-3 trial)	Progressive free: 0.77‡ Progressive disease: 0.68‡	Utilities not used by the company in the model
TA562[22]	Cost-utility analysis of encorafenib with binimetinib versus dabrafenib with trametinib as a 1L or 2L treatment option	People with unresectable or metastatic BRAF V600 mutation positive melanoma	Unclear	EQ-5D-5L (from COLUMBUS trial) mapped to 3L	Progression free: • Encorafenib + binimetinib: 0.78 • Dabrafenib + trametinib: 0.80 Progressive disease: 0.68	Progression free: 0.79‡ Progressive disease: 0.68‡
NICE guideline 14[14]	N/a	Melanoma in children, young people, and adults		EQ-5D (unweighted mean values using utility values from multiple TAs)	Progressive free: 0.7977 Progressive disease: 0.6885	Utilities not used by the company in the model

BSC - best supportive care; DTIC - dacarbazine; EORTC QLQ-30 - European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core30; EQ-5D - EuroQol 5-Dimensions; EQ-5D-3L - EuroQol 5-Dimension 3-Level; GHS - Global Health Status; HRQoL – health-related quality of life; ITT - intention to treat; MEK - mitogen-activated protein kinase; NCT - National Clinical Trial; PRO - patient reported outcomes; QOL - quality of life; SD - standard deviation; TA - Technology Appraisal; TIL-NKI/CCIT - tumour-infiltrating lymphocytes from the Netherlands cancer institute/centre for cancer immune therapy; VAS - visual analogue scale.

** Global health and functional domains*

† Corresponds to the unweighted average of the utilities reported for the progressive disease health state in this appraisal.

§ The company reports the mean baseline EQ-5D-3L as corresponding to the progression-free disease utility.

‡ Corresponds to the unweighted average of the utilities reported for the same health state in this appraisal.

a The EAG notes that the company has reported the wrong values for the stable disease (baseline). The values reported here were obtained directly from the original source; b The EAG notes that the company has reported this appraisal as being in 2L patients. However, the FAD mentions that the key evidence from the BREAK-3 trial, which was in 'previously untreated' (1L) patients.

For the progression-free state, the company included the utility values from TA268, TA269, TA319, TA321, TA357, TA366, TA384, TA396, TA400, TA562, ten Ham *et al.* and Retel *et al.*, whilst for the post-progression state only TA268, TA269, TA321, TA357, TA396, TA562 and Retel *et al.* were used in the calculations. Based on unweighted means from these sources, the model applies a utility value of 0.77 for the PF state and 0.67 for the PD state.

The company's model includes the adjustment of utility values for increasing age using EQ-5D-3L estimates for the UK general population estimates reported by Hernandez Alava *et al.*[71] The model also assumes that lifileucel-infused and ipilimumab-treated patients who remain alive and progression-free after 3 years are cured and subsequently experience the same level of HRQoL as the general population. This assumption is not applied to patients in the BSC or chemotherapy comparator groups, or for patients in the lifileucel group who discontinue therapy or receive an out-of-specification infusion.

The CS[1] includes scenario analyses which apply health state utility values from Retel *et al.* (PF = 0.85, PD = 0.59) and TA357 (PF = 0.74, PD = 0.69). Following the clarification round (clarification response, question B12),[27] the company included an additional scenario analysis whereby the utility values from Retel *et al.*, TA269 and TA319 were excluded from the unweighted mean estimates (PF = 0.76, PD = 0.70).

5.2.4.4.2 QALY loss due to lifileucel administration

The model applies a disutility of -0.09 associated with the lifileucel administration, based on values taken from NICE TA975.[99] This disutility estimate was informed by two studies: Sung *et al.*,[73] which is a model-based decision analysis of allogeneic bone marrow transplantation for young adults with acute myeloid leukaemia (AML), and Kelly *et al.*,[74] which is a model-based decision analysis of cranial radiation analysis for paediatric patients with T-cell acute lymphoblastic leukaemia (ALL). The company's calculations apply the ratio between the disutility associated with AEs of -0.42 from Sung *et al.* and the utility value for event-free health state of 0.91 from Kelly *et al.* (ratio = 0.46), and assume that the *"proportional decrease in utility due to treatment administration [from the CAR-T treatment] compared to event-free survival"* is a proxy to the short-lived decrement in HRQoL expected for patients undergoing lifileucel administration (see CS,[1] Section 3.4.6). The company also assumed that this proportional utility decrement is incurred only by 20% of patients receiving the lifileucel infusion, which corresponds to those patients who require an intensive care unit (ICU) stay after receiving the lifileucel infusion, based on expert clinical opinion obtained by the company.[26] The remaining 80% of patients are assumed to incur zero disutility related to lifileucel infusion. The resulting net disutility of -0.09 is applied to the lifileucel treatment group in the first model cycle and is assumed to have a duration of 1 week.

5.2.4.4.3 QALY losses due to AEs

The company's model includes QALY losses associated with Grade ≥3 AEs occurring with an incidence ≥5% in any of the treatment groups. Disutility values were taken from previous NICE TAs, literature and assumptions (see Table 39). Overall disutilities attributable to AEs were estimated to be [redacted] for lifileucel, -0.015 for ipilimumab, and -0.026 for chemotherapy, which are applied in the first model cycle and are assumed to last for one week. The model assumes that patients receiving BSC do not incur any QALY losses due to AEs.

Table 39: AE disutility values and total disutilities applied in the company's base case model, by treatment group

AE	Frequency	Disutility	Source of disutility	Total disutility			
				Lifileucel	Ipilimumab	Chemotherapy	BSC
Thrombocytopenia	See Table 36	0.09	TA893,[88] Nafees *et al.*[98]	[redacted]	0.001	0.002	0.000
Anaemia		0.09	Beusterien *et al.*[97]		0.001	0.002	
Neutropenia		0.09	Assumed equal to thrombocytopenia		0.000	0.001	
Lymphopenia		0.09	Assumed equal to thrombocytopenia		0.000	0.000	
Leukopenia		0.09	Assumed equal to thrombocytopenia		0.000	0.000	
Febrile neutropenia		0.09	Assumed equal to thrombocytopenia		0.000	0.005	
Hypophosphatemia		0.07	TA893,[88] TA783[100]		0.000	0.000	
Hypoxia		0.22	Lachaine *et al.*[101]		0.000	0.000	
Hypotension		0.07	Assumed equal to hypophosphatemia		0.000	0.000	
Pyrexia		0.11	Beusterien *et al.*[97]		0.000	0.006	
Hypertension		0.07	Assumed equal to hypotension		0.000	0.004	
Rash maculo-papular		0.03	TA950,[89] Paly *et al.*[63]		0.000	0.002	
Chills		0.11	Assumed equal to pyrexia		0.000	0.006	
Diarrhoea or colitis		0.01	TA950,[89] TA384,[66] Beusterien *et al.*[97]		0.002	0.000	
Increased ALT or AST		0.05	TA950,[89] Barbier *et al.*[102]		0.005	0.000	
Hypophysitis		0.13	Middleton *et al.*[103]		0.007	0.000	
Total					**0.015**	**0.026**	**0.000**

AE - adverse event; ALT - alanine aminotransferase; AST - aspartate aminotransferase; BSC - best supportive care; TA - Technology Appraisal

5.2.4.5 Resources and costs

The model includes costs associated with: (i) drug acquisition; (ii) drug administration; (iii) disease management; (iv) management of AEs; and (v) end-of-life (terminal care) costs. Table 40 summarises the costs in the company's base case analysis; each category of costs is described in more detail in the subsequent sections.

Table 40: Summary of costs for all treatment options included in the company's model

Cost parameter	Lifileucel	Ipilimumab	Chemotherapy	BSC
Drug costs (one-off or per 1-week cycle, includes RDI)	[redacted]	£20,070‡§ / £12,042†	£175	£0
Administration costs (one-off or per 1-week cycle)	[redacted]	£509‡ / £430§ / £258†	£1,136	£0
Disease management – progression-free (per 1-week cycle)	£121 / £0‡	£121 / £0‡	£121	£121
Disease management – progressed disease (per 1-week cycle)	£387			
AEs	[redacted]	£1,110	£553	£0
End-of-life care (once-only)	£7,428			

AE - adverse event; RDI - relative dose intensity; BSC - best supportive care
‡ Patients in progression-free state after 3 years are assumed not to incur in further PF disease management costs whilst remaining in this health state
‡ Administration cost applied for the first dose
§ Administration cost applied for second and subsequent doses (except last dose, where applicable)
† Administration cost applied for last dose
a For patients who receive the lifileucel within product specifications
b For patients who receive the lifileucel outside product specifications
c For patients who discontinue the lifileucel regimen before receiving the lifileucel infusion
d For patients who die before receiving the lifileucel infusion

5.2.4.5.1 Drug acquisition and administration costs

Within the company's model, the approach used to estimate drug costs differs by treatment group. The acquisition and administration costs for the therapies included in the model are summarised in Table 41. The derivation of these costs is described in further detail in the subsequent sections.

Table 41: Dosing, treatment schedules and drug cost per cycle included in the company's model

Regimen	Regiment component	% treatment allocation	Admin route	Dosing schedule	RDI	N. of admin per cycle	N. of cycles/ days	Drug/ procedure costs per admin‡	Admin costs per admin	Drug/procedure costs, one-off or per cycle*	Admin costs, one-off or per cycle*
Lifileucel (within specification regimen)	Tumour tissue procurement	100.0%	-	-	-	-	[redacted]	[redacted]	-	[redacted]	-
	LD regimen	100.0%	IV	CP: 60mg/kg daily for 2 days; mesna: 60% of the cyclophosphamide dose; FA: 25mg/m^2 daily for 5 days	CP: 98.2%; mesna: 100%; FA: 87.4%	CP: 2; mesna: 2; FA: 5	1	CP: £72; mesna: £101; FA: £119	£535	CP: £144; mesna: £201; FA: £594 (total: £940)	[redacted]
	Lifileucel infusion	100.0%	IV	[redacted]	-	1	1	[redacted]	£535	[redacted]	[redacted]
	Post-lifileucel infusion	[redacted]	IV	600,000 IU/kg W8h-W12h for up to 6 infusions over approximately 4 days	97.71%	6	1	£1,908.00	£8,836	[redacted]	[redacted]
Total cost lifileucel (within specification regimen)										[redacted]	[redacted]
Lifileucel (outside specification regimen)	Tumour tissue procurement	100.0%	-	-	-	-	[redacted]	[redacted]	-	[redacted]	-
	LD regimen	100.0%	IV	CP: 60mg/kg daily for 2 days; mesna: 60% of the cyclophosphamide dose; FA: 25mg/m^2 daily for 5 days	CP: 98.2%; mesna: 100.0%; FA: 87.4%	CP: 2; mesna: 2; FA: 5	1	CP: £72; mesna: £101; FA: £119	£535	CP: £144; mesna: £201; FA: £594 (total: £940)	[redacted]
	Lifileucel infusion	0.0%※	-	-	-	-	-	£0※	£0※	£0※	£0※
	Post-lifileucel infusion	[redacted]	IV	600,000 IU/kg W8h-W12h for up to 6 infusions over approximately 4 days	97.71%	6	1	£1,908	£8,836	[redacted]	[redacted]
Total cost lifileucel (outside of specification regimen)										[redacted]	[redacted]
Lifileucel (discontinued before infusion)	Tumour tissue procurement	100.0%	-	-	-	-	[redacted]	[redacted]	-	[redacted]	-
	LD regimen	[redacted]	IV	CP: 60mg/kg daily for 2 days; mesna: 60% of the cyclophosphamide dose; FA:	CP: 98.2%; mesna: 100.0%; FA: 87.4%	CP: 2; mesna: 2; FA: 5	1	CP: £72; mesna: £101; FA: £119	£535	CP: [redacted]; mesna: [redacted]; FA: [redacted] (total: [redacted])	[redacted]

Regimen	Regiment component	% treatment allocation	Admin route	Dosing schedule	RDI	N. of admin per cycle	N. of cycles/ days	Drug/ procedure costs per admin‡	Admin costs per admin	Drug/procedure costs, one-off or per cycle*	Admin costs, one-off or per cycle*
				25mg/m^2 daily for 5 days							
Total cost lifileucel (discontinued before infusion)										[redacted]	[redacted]
Lifileucel (died before infusion)	Tumour tissue procurement	100.0%	-	-	-	-	[redacted]	[redacted]	-	[redacted]	[redacted]
Total cost lifileucel (died before infusion)										[redacted]	[redacted]
Ipilimumab	-	100.0%	IV	3mg/kg on D1 Q3W for a total of 3.6 doses	100.0%	1	3.6	£20,070‡§ / £12,042†	£509‡ / £430§ / £258†	£20,070‡§ / £12,042†	£509‡ / £430§ / £258†
Chemotherapy	Dacarbazine	65.0%	IV	850mg/m^2 on D1. then Q3W	96.0%	1	2.16	£93	£509‡ / £430†	£130*	£655
	Temozolomide	10.0%	Oral	200mg/m^2 orally for 5 days Q4W	99.0%	5	1.62	£51	£283⁂	£8*	£229
	Carboplatin	5.0%	IV	AUC 5mg/ml x min on D1 of Q3W cycle	100.0%	1	2.16	£35	£509‡ / £430†	£4*	£50
	Carboplatin + paclitaxel	10.0%	IV	Carboplatin: AUC 5mg/ml x min on D1 of Q3W cycle; paclitaxel: 125mg/m^2 on D1 of Q3W cycle	100.0%	1	2.16	£71	£509‡ / £430†	£15*	£101
	Dacarbazine + cisplatin	10.0%	IV	Dacarbazine: 350mg/m^2/day on D1 of Q3W cycle for 4 cycles; cisplatin: 50mg/m^2/day on D1 of Q3W cycle for 4 cycles	100.0%	1	2.16	£79	£509‡ / £430†	£17.03*	£101
Total chemotherapy										**£175**	**£1,136**
BSC	-	-	-	-	-					**£0**	**£0**

Admin - administration; AUC - area under the curve; CP - cyclophosphamide; D1 - day one; FA - fludarabine; IV - intravenous; LD - lymphodepletion; N - number; RDI - relative dose intensity; Q3W - every three weeks

‡ These values include the application of wastage, RDI, and number of admins per treatment cycle, but not total number of doses/cycles or treatment allocation

** These values include the application of RDI, wastage, number of admins per treatment cycle, total number of doses/cycles, and treatment allocation*

※The company's model assumes that the lifileucel infusion will be provided by the company free of charge.

‡Administration cost applied for the first dose

§ Administration cost applied for second and subsequent doses (except last dose, where applicable)

†Administration cost applied for last dose

⁂ The company applies this administration cost to all days that the patient takes the oral medication. The EAG considers this to be an error; see Section 5.3.5 for further details.

Lifileucel treatment costs

The company's model assumes that the costs of the lifileucel regimen incurred by the NHS depend on whether the patient: (i) receives the full lifileucel regimen within the manufacturing specifications in line with the product's draft SmPC;[13] (ii) receives the full regimen but the infusion was outside of the product specifications; (iii) discontinues the regimen before receiving the lifileucel infusion; or (iv) dies before receiving the lifileucel infusion. The full lifileucel regimen is assumed to include the surgical resection of tumour tissues ('tumour tissue procurement'), the LD chemotherapy regimen, the lifileucel infusion, and the post-infusion IL-2 therapy (see Section 3.2). The dosing schedules, cost allocation and breakdown for each of the components that constitute the lifileucel regimen according to each of the four possible patient infusion outcomes are summarised in Table 41.

The base case model applies the following assumptions for the costs in the lifileucel group:

- [redacted] of patients in whom lifileucel is planned receive the infusion within the SmPC specification.[13] The model assumes that 100% of these patients incur the costs of the tumour tissue procurement, 100% incur the costs of LD chemotherapy, 100% incur the costs of the lifileucel infusion and [redacted] receive incur the costs of IL-2 therapy.
- [redacted] of patients are assumed to receive the infusion outside of the SmPC specification. The model assumes that these patients 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.
- [redacted] of patients are assumed to discontinue the regimen before receiving the lifileucel infusion. 100% of these patients incur the costs of the tumour tissue procurement and 2.5% incur the costs of LD chemotherapy. The costs of the infusion and IL-2 therapy are not incurred by these patients.
- [redacted] of patients are assumed to die before receiving the lifileucel infusion. These patients incur only the costs of the tumour tissue procurement.

The list price for the lifileucel infusion is [redacted]. The company has proposed a PAS which takes the form of a simple price discount of [redacted] The price of the infusion including the PAS is [redacted]. In line with the draft SmPC,[13] lifileucel is assumed to be given at a fixed dose of [redacted]. The costs of administering the lifileucel infusion include one day case attendance (£535.33), based on a weighted average of inpatient day cases related to skin disorders with or without interventions with a

complications and comorbidity (CC) score of 0 to 19+ (codes JD07A to K) from NHS Reference Costs 2023/24,[75] with the weights based on the activity for each code.

The cost of the surgical resection of tumour tissues, which are used in the production of the lifileucel infusion, is assumed to reflect the costs of the hospitalisation period required to carry out the procedure. The cost is based on a weighted mean of elective inpatient costs for a variety of codes from NHS Reference Costs 2023/24,[75] which reflect different resection sites (lung [code YD03Z], lymph node [codes WH54A-B], liver [codes YG10Z and YG11A], musculoskeletal [YH31A and YG11A], skin/subcutaneous [JC42C], breast [YJ09Z], peritoneal/retroperitoneal [YL20A], other visceral and other), with the weights corresponding to activity for each code. The EAG notes that for 'other visceral' and 'other' regions, the company assumed that both groups corresponded to the mean cost of the other resection sites, due to the lack of data for these areas.[1] The final cost per day of the procedure was then obtained by re-weighting the weighted cost using the proportion of patients having the tumour resection from each site from Study C-144-01.[28] The company assumes that tumour tissue procurement would require 2 days of hospital stay, which leads to a total cost of [redacted] for the procedure.

The LD chemotherapy regimen is assumed to be given for 7 days before the lifileucel infusion and includes cyclophosphamide (given with mesna) and fludarabine. Cyclophosphamide is assumed to be given via an IV infusion at a dose of 60mg/kg daily for 2 days, whilst mesna is assumed to correspond to 60% of the dose of cyclophosphamide, and fludarabine is assumed to be administered via IV infusion at a dose of 25mg/m^2 daily for 5 days. The dosage schemes are based on Study C-144-01[28] and the SmPC for mesna.[76] Unit costs were taken from the British National Formulary (BNF)[77] and the Commercial Medicines Unit (CMU) electronic Market Information Tool (eMIT).[78] The company estimated the total costs for cyclophosphamide and mesna using the method of moments, whereby the patients' BSA and weight distributions from Study C-144-01[28] were used to estimate the distribution of patients who would receive different vial options for cyclophosphamide (500mg, 1000mg and 2000mg) and mesna (400mg and 1000mg) and their associated costs. The company's base case analysis accounts for wastage as part of these calculations. The RDIs for drugs were sourced from Study C-144-01[28] and additional assumptions. The total acquisition costs were estimated at £143.78 for cyclophosphamide, £201.34 for mesna and £594.47 for fludarabine. The administration costs for the LD regimen include [redacted] days of inpatient stay with the same daily cost of £535.33 as for lifileucel infusion based on NHS Reference Costs 2023/24,[75] which leads to a total administration cost of [redacted]

The costs for IL-2 therapy given following the lifileucel infusion include the administration of aldesleukin at a dosage of 600,000 IU/kg every 8 to 12 hours for up to 6 doses over approximately 3 days, with the dosage scheme based on Study C-144-01.[28] The model assumes that all patients receiving IL-2 therapy receive the maximum number of doses. Unit costs and RDI estimates were obtained from

the BNF[77] and Study C-144-01,[28] respectively. The proportion of patients who receive the lifileucel infusion (within and outside of the product specifications) and go on to receive the IL-2 regimen was also obtained from Study C-144-01.[28] The total acquisition costs were estimated at [redacted] per patient per cycle, and [redacted] for the groups of patients who receive the lifileucel infusion (within and outside of specifications). The administration costs include 10 days of hospitalisation for the administration of the IL-2 regimen and subsequent monitoring. Thirty percent of this hospitalisation duration (3 days) was assumed to be required for therapy receipt, and 70% (7 days) was assumed to be required for subsequent monitoring. Both periods were further divided between ICU (20%) and inpatient stay (80%), based on the expert clinical opinion obtained by the company.[26] Unit costs for the ICU and inpatient daily hospitalisation costs were sourced from NHS Reference Costs 2023/24[75] (weighted mean cost from codes XC01X-07Z and JD07A-JD07K, respectively, with the weights corresponding to the activity for each code). The total ICU costs were estimated at £2,650.78 per patient per cycle for the administration of IL-2 and £6,185.15 for subsequent monitoring. The total administration cost for patients who receive the lifileucel infusion was estimated at [redacted]

Ipilimumab treatment costs

The acquisition and administration costs for ipilimumab are calculated as a function of the dosing schedule from the SmPC for ipilimumab,[68] the patients' weight distribution from Study C-144-01,[28] unit costs from the BNF,[77] the planned number of doses of ipilimumab (N=4.0) from Hodi *et al.* (MDX-010 study),[69] and an assumption that the RDI for ipilimumab is 100%. The company estimated the cost per cycle using the method of moments, using the distribution of patients who would receive different vial options for ipilimumab (50mg and 200mg), and including wastage as part of the base case analysis. The base case model assumes that patients receive 3.6 doses, rather of 4.0 doses, based on the justification that *"not all patients are expected to receive the full four maximum doses due to disease progression or toxicity concerns."*[1]

Ipilimumab administration costs are modelled as a function of the dosing schedule, and the mean number of doses from Hodi *et al.*[68, 69] and an assumption that patients will receive 3.6 doses (as described above). The unit costs for drug administration were based on NHS Reference Costs 2023/24,[75] and are based on chemotherapy delivery as a proxy for the administration costs for IV drugs in the first and subsequent cycles. The model applies the cost of 'Deliver more Complex Parenteral Chemotherapy at First Attendance' (code SB13Z, £508.97) in the first cycle and 'Deliver Subsequent Elements of a Chemotherapy Cycle' (code SB15Z, £430.24) in the subsequent cycles, with the exception of the last cycle, where both drug and administration costs are multiplied by a factor of 0.6 to account the non-integer mean number of cycles. The total per-cycle acquisition and administration costs for ipilimumab are shown in Table 41. These costs are applied every 3 cycles for the total treatment duration (up to 12 weeks).

Following the clarification round, the company updated their approach for estimating the expected costs of ipilimumab (see clarification response,[27] question B15); the company's updated approach is described in Section 5.4.

Chemotherapy costs

The model includes the costs of five chemotherapy regimens: (i) dacarbazine; (ii) temozolomide; (iii) carboplatin; (iv) carboplatin plus paclitaxel, and (v) dacarbazine plus cisplatin. The costs of these regimens were estimated as a function of the individual dosing schedules for each regimen from their respective SmPCs,[79-83] weight and BSA distributions from Study C-144-01,[28] unit costs per pack from the BNF[77] and eMIT,[78] and RDI estimates for dacarbazine, temozolomide and carboplatin from the US FDA,[84] Gogas *et al.*[85] and Lee *et al.*[86] Similar to the approach used to estimate the costs of ipilimumab, the company used the BSA and weight distributions to calculate the distribution of costs by different drug strength options using the method of moments, and estimated the individual costs per cycle for each treatment regimen. The total costs of each regimen were estimated by multiplying the per cycle costs by the total treatment duration, based on the median treatment duration reported by Mangin *et al.*[30] (1.49 months) which was assumed to be the same for all chemotherapy regimens.

Chemotherapy administration costs are modelled as a function of the dosing schedule and number of administrations per treatment regimen, and unit costs from NHS Reference Costs 2023/24.[75] The model applies the same administration costs for IV regimens as those used for ipilimumab 'Deliver more Complex Parenteral Chemotherapy at First Attendance' (code SB13Z, £508.97) in the first cycle and 'Deliver Subsequent Elements of a Chemotherapy Cycle' (code SB15Z, £430.24) in the subsequent cycles, whilst for the only oral therapy (temozolomide), the model applies the costs of 'Deliver exclusively oral chemotherapy' (code SB11Z, £283.17). The EAG notes that the company's original model applies the administration cost for temozolomide to all days on which the patient takes a pill; this EAG believes this is an error (see Section 5.3.5). The model assumes that for combination chemotherapy regimens, only one administration cost is applied in each regimen cycle. Similar to the acquisition costs, the total administration costs for each regimen were calculated by multiplying the per-cycle costs by the treatment duration of each regimen (1.49 months).

The total acquisition and administration costs for the chemotherapy treatment group were then obtained by calculating the weighted mean costs for all individual chemotherapy regimens, with the weights based on clinical opinion from experts.[26] These costs were applied once-only in the first model cycle. The total acquisition and administration costs per chemotherapy cycle and per chemotherapy regimen are presented in Table 41.

BSC costs

The company's model assumes that patients receiving BSC do not incur any acquisition or administration costs related to active therapy.

Subsequent treatment costs

The company's model does not include any costs related to subsequent-line treatments. The CS[1] states that these were not considered *"due to patients' poor prognosis and lack of treatment options."*

5.2.4.5.2 Disease management costs

HCRU related to the disease management includes the costs associated with medical visits (General Practitioners [GPs], nurses, oncologists, other physicians and healthcare professionals), inpatient care (oncology/general ward and palliative care), home care visits (palliative care physician and nurse, and home aide), different types of blood tests and of imaging tests and pain management treatment. All disease management costs are assumed to be independent of treatment group and vary by health state, with per-cycle costs associated with ongoing disease management being assumed to increase after disease progression. Resource use estimates were based on NICE TA400,[21] with unit costs valued using NHS Reference Costs 2023/2024,[75] PSSRU 2023 and 2014,[87, 104] and NICE TA400.[21]

Table 42 summarises the per-cycle costs for the PF and PD health states included in the company's model. These costs are applied to each corresponding health state in every model cycle, except for patients in the lifileucel and ipilimumab treatment groups who remain progression-free at 3 years onwards as these patients are assumed to be considered cured and are no longer subject to follow-up.

Table 42: Health state disease management resource use and costs used in the model for all treatment groups

Resource component	Resource use frequency (per weekly cycle)		Unit cost (£)	Total cost (per weekly cycle)	
	PF	PD		PF	PD
Medical oncologist visit	0.35	0.13	£193.39	£67.06	£24.96
Radiation oncologist visit	0.01	0.02	£159.94	£2.21	£3.86
GP visit	0.02	0.34	£38.00	£0.70	£13.04
Palliative care physician visit	0.00	0.06	£167.50	£0.00	£10.64
Psychologist visit	0.00	0.02	£167.20	£0.00	£4.04
Plastic surgeon visit	0.01	0.00	£160.87	£1.11	£0.00
Nurse visit	0.03	0.00	£58.11	£1.67	£0.00
Inpatient care - oncology/general ward*	0.01	0.11	£367.08	£5.49	£39.54
Inpatient care - Palliative care unit (days per patient – clarification response, question B17)[27]	0.00	0.23	£305.00	£0.00	£68.79

Resource component	Resource use frequency (per weekly cycle)		Unit cost (£)	Total cost (per weekly cycle)	
	PF	**PD**		**PF**	**PD**
Palliative care physician visit - home care	0.00	0.05	£92.00	£0.00	£4.62
Palliative care nurse visit - home care	0.00	0.20	£142.34	£0.00	£27.98
Home aide visits	0.00	0.43	£243.00	£0.00	£104.11
CT scan	0.23	0.01	£113.71	£26.17	£0.99
MRI of brain	0.01	0.00	£171.92	£2.14	£0.51
Chest X-ray	0.07	0.00	£168.16	£11.71	£0.50
PET scan	0.00	0.00	£613.44	£0.00	£0.00
Bone scintigraphy	0.00	0.00	£498.45	£0.34	£0.00
Echography	0.01	0.00	£123.07	£0.76	£0.00
Complete blood count	0.30	0.00	£3.10	£0.93	£0.00
Complete metabolic panel	0.28	0.00	£1.53	£0.43	£0.00
Lactate dehydrogenase	0.28	0.00	£1.53	£0.43	£0.00
Pain management	0.00	0.39	£211.48	£0.00	£83.47
Total				**£121.16**	**£387.06**

GP - General Practitioner; MRI - magnetic resonance imaging; CT - computerised tomography; PF - progression free state; PD - progressed disease
**Days per patient (clarification response,[27] question B17)*

5.2.4.5.3 AE management costs

The model includes the costs associated with the management of Grade ≥3 AEs with an incidence ≥5% observed in any of the treatment groups. Unit costs were taken from NHS Reference Costs 2023/24,[75] previous NICE TAs (TA893, TA366, TA950 and TA319), Lorigan *et al.*[90] and clinical expert opinion.[26] Unit costs and total costs by treatment group used in the model are summarised in Table 43. AE management costs per patient are estimated to be [redacted] for lifileucel, £1,110.29 for ipilimumab and £553.19 for chemotherapy. These costs are applied once-only during the first model cycle. Patients in the BSC treatment group are assumed not to incur any costs related to AEs.

Table 43: AE costs used in the model, by treatment group

AE	AE frequencies	Unit cost (£)	Source of unit costs	Total cost (£)			
				Lifileucel	Ipilimumab	Chemotherapy	BSC
Thrombocytopenia	See Table 36	346.38	NHS Reference Costs 23/24[75] (codes SA12G-K), TA893[88]	[redacted]	3.46	6.10	0.00
Anaemia		392.70	NHS Reference Costs 23/24[75] (codes SA01G– SA01K, SA03G–SA03H, SA04G–SA04L, SA05G–SA05J), TA893[88]		3.93	10.37	
Neutropenia		388.39	NHS Reference Costs 23/24[75] (codes SA35A–E), TA893[88]		0.00	5.13	
Lymphopenia		411.53	NHS Reference Costs 23/24[75] (codes SA08G-J), TA893[88]		0.00	0.00	
Leukopenia		411.53	NHS Reference Costs 23/24[75] (codes SA08G-J), TA893[88]		0.00	0.00	
Febrile neutropenia		2,058.10	NHS Reference Costs 23/24[75] (codes SA08G-J), TA893[88]		0.00	102.90	
Hypophosphatemia		459.29	NHS Reference Costs 23/24[75] (codes KC05G-N), TA893[88]		0.00	0.00	
Hypoxia		483.45	NHS Reference Costs 23/24[75] (codes DZ27N-U), TA893[88]		0.00	0.00	
Hypotension		411.53	NHS Reference Costs 23/24[75] (codes SA08G-J), TA893[88]		0.00	0.00	
Pyrexia		4,262.89	TA366,[19] NHSCII index[87]		0.00	213.14	
Hypertension		361.00	NHS Reference Costs 23/24[75] (code EB04Z), TA893[88]		0.00	18.05	
Rash maculo-papular		462.78	NHS Reference Costs 23/24[75] (codes JD07E-K), TA893[88]		4.63	23.14	
Chills		3,487.13	NHS Reference Costs 23/24[75] (codes WJ07B-C)		0.00	174.36	
Diarrhoea or colitis		5,162.07	NHS Reference Costs 23/24[75] (see paragraph below), TA950,[89] company's advisory board meeting		1032.41	0.00	
Increased ALT or AST		412.84	NHS Reference Costs 23/24[75] (codes SA08H-J), TA950[89]		37.16	0.00	
Hypophysitis		573.97	TA319,[16] Lorigan *et al.*[90]		28.70	0.00	
Total (£)				[redacted]	**1,110.29**	**553.19**	**0.00**

AE - adverse event; ALT - alanine aminotransferase; AST - aspartate aminotransferase; BSC - best supportive care; NHSCII - NHS Cost Inflation Index; TA - Technology Appraisal

The model includes the costs associated with diarrhoea or colitis which are intended to reflect long-term complications associated with treatment using ICIs. The company's calculations used to estimate these costs are summarised in Table 44. The model assumes that [redacted] of patients receiving lifileucel and 20% receiving ipilimumab would experience these Grade 3/4 immune-related gastrointestinal reactions. Patients are assumed to be managed initially with corticosteroids, based on five days of hospitalisation for treatment with high-dose steroids, which were sourced from the NHS Reference Costs 2023/24[75] (non-elective short stay, codes FD10A-M) and length of stay based on the expert clinical opinion.[70] The CS[1] states that 20% of patients treated with corticosteroids would require additional treatment with infliximab due to becoming corticosteroid-refractory, and that 80% of patients receiving infliximab would also require further treatment with vedolizumab (see clarification response,[27] question B20). The acquisition and administration costs for these drug therapies were based on the SmPCs for infliximab and vedolizumab,[105, 106] clinical opinion obtained during the company's advisory board meeting,[26] the BNF,[77] NHS Reference Costs 2023/24[75] and assumptions. The model also includes the costs of endoscopic examination incurred by 30% of patients receiving infliximab (clarification response,[27] question B20), with unit costs taken from NHS Reference Costs 2023/24.[75] The total cost of diarrhoea or colitis was estimated at £5,162.07.

Table 44: Costs for diarrhoea and colitis used in the model

Treatment	Management component	% patients receiving component	Length of stay/ no. doses	Unit costs (per day, per pack or per admin)	Total cost per patient (£)	Total cost (£)	Sources
Initial treatment with corticosteroids	hospitalisation	100%	5 days	567	2,834	2,834	NHS Reference Costs 2023/24[75] (codes FD10A-M, Non-elective short stay), company's advisory board[26]
Treatment with infliximab (5mg/kg)	acquisition costs	20%	1.5 doses	377	2,289†	458	Infliximab SmPC,[105] company's advisory board, [26] BNF,[77] NHS Reference Costs 2023/24[75] and assumptions
	admin costs (inpatient care)			536	803	161	
Sub-total infliximab						618	
Treatment with vedolizumab (300mg)	acquisition costs	16%‡	4 doses	2,050	8,200⁑	1,312	Vedolizumab SmPC,[106] company's advisory board,[26] BNF, [77] NHS Reference Costs 2023/24,[75] and assumptions
	admin costs (inpatient care)			536	2,141	343	
Sub-total vedolizumab						1,655	
Endoscopy	-	6%§	1	915	915	55	NHS Reference Costs 2023/24[75] (codes FE01Z - FE50B, total cost), company's advisory board[26]
Total						**5,162**	-

Admin – administration; BNF - British National Formulary
†Based on the mean weight of [redacted] from cohorts 2 and 4 in the C-144-01 study, the dosage schedule of 5mg/kg per dose, treatment regimen of 1.5 doses and a unit size of 100mg per unit, which generates an acquisition cost per dose of [redacted].
⁑ Based on the dosage schedule of 300mg per dose, treatment regimen of 4 doses and a unit size of 300mg per unit, which leads to an acquisition cost per dose of £2,050.00.
‡ Based on 80% of patients receiving infliximab; § Based on 30% of patients receiving infliximab.

5.2.4.5.4 End-of-life care costs

The cost of end-of-life care was estimated to be £7,428.05 per patient. This cost is applied once-only at the point of patient death. This cost was based on the value reported in NICE TA627,[107] which in turn used the mean cost values related to health and social care for four different types of cancer (breast, colorectal, lung and prostate) reported in Round *et al.*[91] The cost estimate reported in TA627 at 2018 prices (£6,361.77) was uplifted by the company to 2023/24 prices using the NHS Cost Inflation Index (NHSCII) taken from PSSRU 2023.[87]

5.2.5 Model evaluation methods

The CS[1] presents pairwise cost-effectiveness results for (STC-adjusted) lifileucel versus ipilimumab, (unadjusted) lifileucel versus chemotherapy and (unadjusted) lifileucel versus BSC. ICERs are presented using both the deterministic and probabilistic versions of the model. The probabilistic ICER is based on 1,000 Monte Carlo simulations. The results of the probabilistic sensitivity analysis (PSA) are presented using cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs). All model results presented in the CS include the PAS price for lifileucel and the list prices for other treatments. All results presented in the CS include a decision modifier of 1.7 (applied to the incremental QALY gains), although the EAG notes that the York QALY Shortfall Calculator[108] suggests that a modifier of 1.2 should be applied in the comparison against ipilimumab; this issue is discussed further in Section 5.3.5.

The CS[1] presents the results of deterministic sensitivity analyses (DSAs) using both tornado plots and tables. The CS also presents the results of 15 scenario analyses which explore: alternative discontinuation rates; an assumption that patients who do not have the lifileucel infusion receive BSC only; the use of non-reference case discount rates of 1.5% for health outcomes and costs; the inclusion of a 5-year cure time point; the use of selected alternative parametric survival models for PFS and OS; the inclusion of a higher SMR of 1.57; the impact of excluding drug wastage costs; a higher number of doses of ipilimumab and alternative utility values.

5.2.6 Company's cost effectiveness results

5.2.6.1 Company's central estimates of cost-effectiveness

The company's central estimates of cost-effectiveness are presented in Table 45. The results are presented here as pairwise comparisons of lifileucel versus each comparator. This is because the model includes STC-adjustment in the comparison of lifileucel versus ipilimumab, but no adjustment for the comparisons against chemotherapy and BSC. This precludes the use of a single, coherent, fully incremental analysis of all options. All results presented here include the PAS discount for lifileucel and the list prices for comparators. The results of the economic analyses including comparator PAS discounts are available in a separate confidential appendix. All results presented here include a decision

modifier of 1.7 for all comparisons, as per the results presented in the CS. However, the EAG believes that the appropriate decision modifier for the comparison against ipilimumab is 1.2 (see Section 5.3.5).

Lifileucel versus ipilimumab (STC-adjusted comparison)

The probabilistic version of the company's model suggests that compared against ipilimumab, lifileucel is expected to generate an additional 3.73 QALYs at an additional cost of [redacted]; the corresponding pairwise ICER is expected to be [redacted] per QALY gained. When QALY weighting is included in the analysis (decision modifier = 1.7), the ICER for lifileucel is expected to be [redacted] per QALY gained.

Lifileucel versus chemotherapy (naïve ITC)

The probabilistic version of the company's model suggests that compared against chemotherapy, lifileucel is expected to generate an additional 2.69 QALYs at an additional cost of [redacted]; the corresponding pairwise ICER is expected to be [redacted] per QALY gained. When QALY weighting is included in the analysis (decision modifier = 1.7), the ICER for lifileucel is expected to be [redacted] per QALY gained.

Lifileucel versus BSC (naïve ITC)

The probabilistic version of the company's model suggests that compared against chemotherapy, lifileucel is expected to generate an additional 2.97 QALYs at an additional cost of [redacted]; the corresponding pairwise ICER is expected to be [redacted] per QALY gained. When QALY weighting is included in the analysis (decision modifier = 1.7), the ICER for lifileucel is expected to be [redacted] per QALY gained.

For all three comparisons, the deterministic ICERs are around £3,000 to £6,000 higher than the probabilistic ICERs. Owing to problems in the company's PSA, the EAG considers the results of the deterministic model to be more reliable than those obtained from the probabilistic model (see Section 5.3.5).

Table 45: Company's base case results, lifileucel versus comparators, pairwise

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER (excl. DM)	ICER (DM)
Probabilistic model								
Lifileucel (STC-adjusted) versus ipilimumab (DM=1.7)								
Lifileucel	NR	4.61	[redacted]	NR	3.73	[redacted]	[redacted]	[redacted]
Ipilimumab	NR	0.88	[redacted]	NR	-	-	-	-
Lifileucel (unadjusted) versus chemotherapy (DM=1.7)								
Lifileucel	NR	3.26	[redacted]	NR	2.69	[redacted]	[redacted]	[redacted]
Chemotherapy	NR	0.57	[redacted]	NR	-	-	-	-
Lifileucel (unadjusted) versus BSC (DM=1.7)								
Lifileucel	NR	3.26	[redacted]	NR	2.97	[redacted]	[redacted]	[redacted]
BSC	NR	0.29	[redacted]	NR	-	-	-	-
Deterministic model								
Lifileucel (STC-adjusted) versus ipilimumab (DM=1.7)								
Lifileucel	8.44	4.45	[redacted]	7.12	3.58	[redacted]	[redacted]	[redacted]
Ipilimumab	1.32	0.88	[redacted]	-	-	-	-	-
Lifileucel (unadjusted) versus chemotherapy (DM=1.7)								
Lifileucel	5.73	3.09	[redacted]	4.93	2.53	[redacted]	[redacted]	[redacted]
Chemotherapy	0.79	0.56	[redacted]	-	-	-	-	-
Lifileucel (unadjusted) versus BSC (DM=1.7)								
Lifileucel	5.73	3.09	[redacted]	5.32	2.80	[redacted]	[redacted]	[redacted]
BSC	0.41	0.29	[redacted]	-	-	-	-	-

** Undiscounted*

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; DM - decision modifier; Inc. - incremental; NR - not reported

5.2.6.2 Company's PSA results

CEACs for the comparisons of lifileucel versus ipilimumab, chemotherapy and BSC are presented in Figure 29, Figure 30, Figure 31, respectively. Assuming willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY gained, the probability that lifileucel generates more net benefit than ipilimumab is estimated to be approximately [redacted] and [redacted], respectively. At these same WTP thresholds, the probability that lifileucel generates more net benefit than chemotherapy and BSC is estimated to be approximately [redacted].

Figure 29: CEACs, lifileucel (STC-adjusted) versus ipilimumab, pairwise, including decision modifier of 1.7 (re-drawn by the EAG)

Figure 30: CEACs, lifileucel versus chemotherapy, pairwise, including decision modifier of 1.7 (re-drawn by the EAG)

Figure 31: CEACs, lifileucel versus BSC, pairwise, including decision modifier of 1.7 (re-drawn by the EAG)

5.2.6.3 Company's DSA results

Tornado plots summarising the results of the company's DSAs are presented in Figure 32, Figure 33 and Figure 34, respectively. Across all three comparisons, the model is most sensitive to the parameters of the survival models for PFS and OS, and the utility values for the PF and PD health states. For the comparison of lifileucel versus ipilimumab, the ICER is also sensitive to the per-cycle costs of disease management in the PD state.

Figure 32: DSA results, lifileucel (STC-adjusted) versus ipilimumab, pairwise, including decision modifier of 1.7 (reproduced from the company's model)

Figure 33: DSA results, lifileucel versus chemotherapy, pairwise, including decision modifier of 1.7 (reproduced from the company's model)

Figure 34: DSA results, lifileucel versus BSC, pairwise, including decision modifier of 1.7 (reproduced from the company's model)

5.2.6.4 Company's scenario analyses results

The results of the company's scenario analyses for all comparisons are summarised in Table 46. The scenario analyses indicate the following:

- The ICERs for lifileucel versus ipilimumab range from [redacted] to [redacted] per QALY gained.
- The ICERs for lifileucel versus chemotherapy range from [redacted] to [redacted] per QALY gained.
- The ICERs for lifileucel versus BSC range from [redacted] to [redacted] per QALY gained.

For all three comparisons, the lowest ICERs relate to scenarios in which non-Reference Case discount rates of 1.5% are used. The EAG's concerns regarding the applicability of these lower discount rates are discussed in Section 5.3.5.

Table 46: Company's scenario analysis results, lifileucel versus comparators, pairwise, deterministic, includes decision modifier of 1.7

Scenario	Lifileucel (STC-adjusted) vs. ipilimumab	Lifileucel vs. chemotherapy	Lifileucel vs. BSC
Company's base case model (deterministic)	[redacted]	[redacted]	[redacted]
FAS discontinuation*	[redacted]	[redacted]	[redacted]
BSC only after lifileucel discontinuation	[redacted]	[redacted]	[redacted]
1.5% discount rates	[redacted]	[redacted]	[redacted]
5-year cure time point	[redacted]	[redacted]	[redacted]
Lifileucel PFS - exponential MCM	[redacted]	[redacted]	[redacted]
Lifileucel PFS & OS - log-logistic MCM	[redacted]	[redacted]	[redacted]
Ipilimumab PFS - generalised gamma	[redacted]	[redacted]	[redacted]
Ipilimumab OS - log-logistic	[redacted]	[redacted]	[redacted]
Chemotherapy PFS - log-normal	[redacted]	[redacted]	[redacted]
Chemotherapy OS - log-logistic	[redacted]	[redacted]	[redacted]
SMR=1.57	[redacted]	[redacted]	[redacted]
No wastage (vial sharing)	[redacted]	[redacted]	[redacted]
Ipilimumab 4 doses	[redacted]	[redacted]	[redacted]
Utility values from Retel *et al.* (2018)	[redacted]	[redacted]	[redacted]
Utility values from TA357	[redacted]	[redacted]	[redacted]

STC - simulated treatment comparison; DM - decision modifier; FAS - Full Analysis Set; BSC - best supportive care; MCM - mixture-cure model; PFS - progression-free survival; OS - overall survival; SMR - standardised mortality ratio; TA - Technology Appraisal
** The EAG was unable to replicate this figure directly using the model. Reported ICERs are based on the CS.*

5.3 Critical appraisal of the company's economic analysis

This section presents the EAG's critical appraisal of the company's original economic model, as described in the CS.[1] Section 5.3.1 summarises the EAG's methods for the critical appraisal of the company's model. Section 5.3.2 describes the EAG's verification of the company's model. Section 5.3.3 describes the correspondence between the CS, the model inputs and their original sources. Section 5.3.4 describes the extent to which the company's economic analysis adheres to the NICE Reference Case.[109] Section 5.3.5 presents the main issues identified during the EAG's critical appraisal of the company's model.

5.3.1 Critical appraisal methods

The EAG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic analysis and the underlying economic model upon which this is based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists.[60, 110]
- Scrutiny and discussion of the company's model by the EAG.
- Double-programming of the deterministic version of the company's original model to fully assess the logic of the model structure, to draw out any unwritten assumptions and to identify any apparent errors in model implementation.

- Examination of the correspondence between the description of the model reported in the CS[1] and the company's executable model.
- Where possible, checking parameter values used in the company's model against their original data sources.
- Replication of the base case results, PSA, DSAs and scenario analyses reported in the CS using the company's executable model.
- The use of expert clinical input to judge the credibility of the company's economic analyses and the assumptions underpinning the model.

5.3.2 Model verification by the EAG

Table 47 presents a comparison of the results of the deterministic version of the company's original model and the EAG's double-programmed model. As shown in the table, the results obtained from the EAG's rebuilt model are similar to those generated using the company's model. However, the EAG's double-programming exercise revealed several minor programming errors; these issues are discussed in detail in Section 5.3.5 (critical appraisal point 1).

Table 47: Comparison of results generated using the company's original model and the EAG's double-programmed model, including lifileucel PAS, excludes QALY weighting, excludes correction of errors, deterministic

Option	EAG's double-programmed model			Company's model		
	LYGs*	QALYs	Costs	LYGs*	QALYs	Costs
Lifileucel (STC-adjusted)	8.44	4.44	[redacted]	8.44	4.45	[redacted]
Lifileucel (STC-unadjusted)	5.73	3.09	[redacted]	5.73	3.09	[redacted]
Ipilimumab	1.32	0.88	[redacted]	1.32	0.88	[redacted]
Chemotherapy	0.79	0.56	[redacted]	0.79	0.56	[redacted]
BSC	0.41	0.29	[redacted]	0.41	0.29	[redacted]

EAG - External Assessment Group; PAS - Patient Access Scheme; LYG - life year gained; QALY - quality-adjusted life year; BSC - best supportive care
** Undiscounted*

5.3.3 Correspondence between the model, the CS and original sources of parameter values

Where possible, the EAG checked the company's model input values against their original sources, including published sources and additional sources provided by the company such as the Study C-144-01 Clinical Study Report (CSR).[28] The EAG did not identify any key remaining inconsistencies of relevance in the revised version of the company's model submitted following the clarification round. Nonetheless, the EAG notes that the incidence rate of Grade 3+ hypophysitis reported in da Silva *et al.*[52] does not correspond to the incidence used in the model by the company for ipilimumab (1.0% vs 5.0%, respectively). This is a minor discrepancy.

5.3.4 Adherence to the NICE Reference Case

Table 48 summarises the extent to which the company's economic model adheres to the NICE Reference Case.[109] The EAG does not believe that there are any major deviations from the Reference Case; however, the EAG does have concerns about the evidence used to inform the model, including the synthesis of clinical evidence the approach taken to estimate health state utility values, and the decision modifier applied in the comparison against ipilimumab.

Table 48: Adherence to the NICE Reference Case

Element of HTA	Reference Case	EAG comments
Defining the decision problem	The scope developed by NICE	The decision problem addressed by the company's economic model is generally in line with the final NICE scope.[29] The population included in the economic model reflects [redacted] This is narrower than the population defined in the NICE scope but is consistent with the anticipated marketing authorisation for lifileucel.[12] Relevant subgroups are not listed in the NICE scope and the CS[1] does not evaluate the cost-effectiveness of lifileucel in any subgroups.
Comparator(s)	As listed in the scope developed by NICE	The company's model includes three comparators: (i) ipilimumab; (ii) chemotherapy and (iii) BSC. The final NICE scope[29] lists individual chemotherapy regimens; however, the company's model evaluates chemotherapy as a basket of treatments based on the assumption that all regimens are clinically equivalent.
Perspective on outcomes	All health effects, whether for patients or, when relevant, carers	The economic analysis adopts an NHS and PSS perspective, including health effects on patients. Impacts on caregivers are not included.
Perspective on costs	NHS and PSS	The model includes costs borne by the NHS and PSS.
Types of economic evaluation	Cost-utility analysis with fully incremental analysis	The company's model adopts a cost-utility approach. The results of the company's base case analyses are presented in terms of pairwise ICERs for lifileucel versus each individual comparator (ipilimumab, chemotherapy and BSC).
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model adopts a lifetime horizon ([redacted] years).
Synthesis of evidence on health effects	Based on systematic review	Study C-144-01[28] is a single-arm study and therefore ITCs were required to estimate relative treatment effects against each comparator. Studies reporting on outcomes for comparators were identified through an SLR. Relative treatment effects for lifileucel versus ipilimumab are estimated using an STC using data from Study C-144-01[28] and da Silva *et al.*[52] The company's model applies the ratio of the STC-adjusted HR and the unadjusted HR to the lifileucel MCMs which results in more favourable outcomes for lifileucel compared with the unadjusted MCMs fitted to data on PFS and OS from Study C-144-01. The comparisons of lifileucel versus chemotherapy were based on a naïve ITC using Mangin *et al.*[30] The NICE Methods Manual[109] states that naïve ITCs comparing individual study arms are not acceptable and that

Element of HTA	Reference Case	EAG comments
		the results of such analyses will be treated as observational in nature and are associated with increased uncertainty.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Health state utility values are based on an unweighted mean of utility values reported in previous economic evaluations and previous NICE TAs of treatments for advanced melanoma. Most but not all of these utility estimates have been measured and valued using the EQ-5D-3L. The EAG's concerns regarding this approach are discussed further in Section 5.3.5, critical appraisal point 7. Disutility values associated with AEs and lifileucel administration are based on published studies and previous NICE TAs.
Source of data for measurement of HRQoL	Reported directly by patients or carers, or both	
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit, except in specific circumstances	The results presented in the CS[1] apply a decision modifier of 1.7 for comparisons of lifileucel versus ipilimumab, chemotherapy and BSC. However, the York Shortfall Calculator[108] suggests that the decision modifier for lifileucel versus ipilimumab is 1.2. This issue is discussed further in Section 5.3.5, critical appraisal point 9.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be values using the prices relevant to the NHS and PSS	Drug costs are valued at current prices. Other resource costs are valued using estimates from NHS Reference Costs 2023/24.[75]
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Health outcomes and costs are discounted at a rate of 3.5% in the company's base case analysis. The CS[1] presents an argument in support of using non-reference case discount rates of 1.5% for health outcomes and costs. The CS reports the results of a scenario analysis which includes these lower discount rates.

NICE - National Institute for Health and Care Excellence; HTA - Health Technology Assessment; EAG - External Assessment Group; NHS - National Health Service; PSS - Personal Social Services; HRQoL - health-related quality of life; QALY - quality-adjusted life year; CS - company's submission; EQ-5D-3L - Euroqol 5-Dimensions 3-Level; ICER - incremental cost-effectiveness ratio; BSC - best supportive care; ITC - indirect treatment comparison STC - simulated treatment comparisons; HR - hazard ratio; MCM - mixture-cure model; PFS - progression-free survival; OS - overall survival; MEK - mitogen-activated protein kinase.

5.3.5 Main issues identified in EAG's critical appraisal

Box 1 summarises the main issues identified within the EAG's critical appraisal of the company's original economic model. These issues are discussed in further detail in the subsequent sections.

Box 1: Main issues identified from the critical appraisal

(1)	Model errors and other minor issues
(2)	Uncertainty around absolute outcomes for adjusted lifileucel MCMs
(3)	Uncertainty relating to the company's survival modelling
(4)	Uncertainty around outcomes for cured patients
(5)	Uncertainty around outcomes for patients who do not receive lifileucel infusion
(6)	Uncertainty around assumed relative treatment effect for BSC versus chemotherapy
(7)	Issues relating to utility values
(8)	Issues relating to costs
(9)	Inappropriate use of a higher decision modifier for ipilimumab
(10)	Poor implementation of PSA
(11)	Relevance of non-reference case discount rates

(1) Model errors and other minor issues

The EAG's double-programming exercise and additional cell-checking revealed several errors in the original version of the company's model. These issues were raised as part of the EAG's clarification letter (see clarification response,[27] questions B15 and questions B23 to B33).

(a) General population mortality risks

The EAG identified three minor errors relating to the company's calculations of general population mortality risks:

(i) The model uses life tables for the UK (2020-2022).[72] The EAG believes that it would be more appropriate to use life tables for England.[111]

(ii) Within the company's model, general population mortality risks per 1-week model cycle are estimated using a weighted survival approach for men and women. However, the initial distribution of men and women (from Study C-144-01[28]) is applied from age zero rather than the population age in the first model cycle (age [redacted] years). Consequently, the distribution of males and females at model entry is not the same as the distribution of males and females in Study C-144-01.

(iii) The model formulae which are used to convert the annual mortality risks by year to 1-week probabilities assume that there are 52 weeks per year. However, there 52.18 weeks per year (i.e., 365.25/7).

(b) Calculation of LYGs and QALYs gained

The model traces for each treatment group calculate the number of LYGs and QALYs gained adjusted for the 1-week cycle length by dividing the variable "cycles" by another variable called "time." The variable "cycles" has a value of [redacted] and the variable "time" has a value of [redacted]. However, [redacted] is not equal to the number of weeks per year (i.e., the formula above gives 52.1875 rather than 52.1785).

(c) Inconsistent number of cycles applied in year 1

The model includes 54 weekly cycles in the first year of the model and 52 or 53 weekly cycles in all other years within the modelled time horizon. This is inconsistent and reflects a minor programming error.

(d) Error in age-adjustment of utility values

The base case model includes age-adjustment of utility values. This is a selectable option within the model which can be disabled. The EAG identified two related problems concerning the implementation of this part of the model:

(i) When the age-adjustment setting is disabled, the formulae which calculate the utility adjustment multiplier at each population age returns the EQ-5D-3L estimate for the general population at age [redacted] years. The formulae should instead return a value of 1.0 for all ages in the model.

(ii) The CS[1] states that the model was intended to include an assumption that ipilimumab- and lifileucel-treated patients who remain alive and progression-free at 3 years rebound to general population utility (i.e., full functional cure). However, the model calculations which estimate QALYs per cycle in the trace instead return a value of 1.0 for all cycles after Year 3 (i.e., perfect health).

(e) Error relating to chemotherapy treatment duration

The model assumes that all chemotherapy regimens are given for a fixed duration of 1.49 months (approximately 45.3 days). The model cost calculations assume that 2.16 x 21-day cycles of dacarbazine can be given in 1.49 months. However, dacarbazine treatment is given on Day 1 of each cycle with the next 20 days off-treatment. Therefore, within the first 1.49 months, patients would have 3 treatment days (on Days 1, 22 and 44) rather than 2.16 treatment days. This issue also affects the estimated costs of drug acquisition and administration for all other chemotherapy regimens included in the model.

(f) Underestimation of number of doses of ipilimumab received

The CS[1] states that patients can receive a maximum of 4 doses of ipilimumab. However, the CS states that due to progression and toxicity, the model instead assumes that patients receive an average of 3.6 doses of ipilimumab, based on Hodi *et al.*[69] The model estimates the costs of receiving 100% and 60%

of a full dose of ipilimumab per 3-week cycle and applies 100% of the cost of a dose in model cycles 0, 3 and 6 and 60% of the cost of a dose in cycle 9. The ipilimumab model trace then multiplies these cycle-specific ipilimumab dose costs by the probability of being alive and progression-free at these time points (based on cumulative survival probabilities of PFS). This results in patients in the model receiving fewer than 3.6 doses of ipilimumab (the company's intended assumption). The company's approach double-counts the impact of progression and other reasons for discontinuation, thereby underestimating the expected costs of ipilimumab acquisition and administration.

(g) Error relating to temozolomide administration costs

The model includes oral temozolomide as one of the regimens which is included in the basket of chemotherapy options. The cost calculations included in the model apply an administration cost for temozolomide of £283.17 on every day that the patient takes a pill. This means that the administration cost for this treatment is applied 8.1 times in 1.49 months. This assumption substantially overestimates the costs of temozolomide administration. Instead, the EAG believes that this administration cost should be included once per chemotherapy cycle.

(h) Programming error relating to the weighted costs of biopsy (part of tumour procurement)

The formulae which are used to calculate the weighted costs for the biopsy on musculoskeletal site (as part of the costs of tumour procurement for patients receiving lifileucel) refers to the wrong column for the number of cases. This is a programming error.

Following the clarification round, the company acknowledged that each of issues (a) to (h) were errors, except for issue (a[ii]). The company's response to clarification question B25 states: *"The proportion of males and females was derived from the C-144-01 trial and assumed to be independent of age."*[27] However, this is not an accurate description of the model programming – the company's model calculations result in the percentage of alive patients who are female at model entry being [redacted], rather than [redacted] (as estimated from Study C-144-01[28]). Following the clarification round, the company provided an updated model which includes the correction of all of the other errors. The EAG notes that the company's updated model corrections do not adequately address issue a[i]. Further details of the changes made in the company's updated model and its results are provided in Section 5.4.

(2) Uncertainty around absolute outcomes for adjusted lifileucel MCMs

The EAG's concerns regarding the robustness of the estimates of relative treatment effects obtained from the company's STC are described in Section 4.6. Owing to the unanchored nature of the comparison, the STC approach generates estimates of the relative effect of lifileucel on PFS and OS in the da Silva *et al.* ipilimumab population.[52] The economic model applies the ratio of STC-adjusted and unadjusted HRs to the lifileucel MCMs for PFS and OS fitted to the Study C-144-01 data.[28] In principle,

raising the lifileucel MCMs to the power of the ratio of HRs results in estimates of the absolute effect of lifileucel had this treatment been included in the da Silva ipilimumab population, which may be different to the estimates obtained by fitting MCMs to the STC-adjusted IPD. The company's selected unadjusted MCMs for lifileucel suggest cure fractions for PFS and OS of [redacted] and [redacted] respectively. Applying the ratio of HRs to the MCMs lifts the PFS and OS curves, leading to implied cure fractions of [redacted] and [redacted], respectively. The EAG notes the following concerns:

- The implied cure fractions from the adjusted MCMs are substantially higher than those estimated using the Study C-144-01 data (the key study included in the CS[1]).
- The adjusted MCMs and the associated implied cure fractions reflect estimates of the absolute treatment effects for lifileucel in the wrong (da Silva) population.
- Clinical input received by the company indicates that a cure fraction of [redacted] is expected for lifileucel-infused patients in the target population. The implied cure fractions for PFS and OS from the adjusted MCMs far exceed this estimate. The EAG has concerns regarding the plausibility of these adjusted model predictions.
- Applying the cure fractions estimated from Study C-144-01 without adjustment will result in a higher ICER than that suggested by the company's base case model.

As a consequence of these issues, the EAG believes that the economic comparison of lifileucel versus ipilimumab presented in the CS[1] should be interpreted with considerable caution.

(3) Uncertainty relating to the company's survival modelling

The EAG has several concerns regarding the company's survival analysis presented in the CS.[1] These concerns are discussed below based on the general considerations around model fitting and selection set out in NICE Decision Support Unit (DSU) Technical Support Documents (TSDs) 14 and 21.[112, 113]

(a) Use of independent versus jointly fitted models

As Study C-144-01[28] was a single-arm study, and data from only one arm was extracted from da Silva *et al.*[52] and Mangin *et al.*,[30] respectively, the company had no option other than to fit models independently to each treatment group. The EAG considers this aspect of the company's survival modelling approach to be appropriate.

(b) Range of models assessed

As noted in Section 5.2.4.2, within the current appraisal, the company fitted standard parametric models to the available data for lifileucel and its comparators but only fitted MCMs for lifileucel. The company discounted all of the standard parametric models for lifileucel because they did not provide a good representation of the observed PFS and OS data (see CS,[1] Figure 18 and Figure 24). Thus, the survivor functions included in the company's base case analysis are MCMs for lifileucel and standard parametric

models for all comparators. The EAG's clinical advisors commented that they believe that lifileucel is expected to lead to long-term survival similar to cure in some patients; hence, the use of MCMs for lifileucel is justified. However, the EAG's clinical advisors also expect that some ipilimumab-treated patients will achieve long-term survival; this expectation was also held by clinical experts who attended the company's advisory board.[26] The EAG asked the company to clarify why MCMs had not been fitted to the ipilimumab group and to consider fitting more flexible models such as spline models (see clarification response,[27] questions B1 and B6). The company's response argues that MCMs would be numerically unstable due to the insufficient follow-up in da Silva *et al.*[52] and stated that implementing spline-based models was infeasible in the time frame provided. NICE TSD21[113] highlights that the reliability of MCMs is dependent on there being sufficient follow-up and numbers of events. However, the EAG notes that the company did not attempt to fit MCMs to the ipilimumab data and so their concern regarding numerically stability appears to be speculative.

The EAG believes that the use of MCMs for the lifileucel group is appropriate but that the use of more flexible parametric models for the ipilimumab and chemotherapy groups may have been better able to reflect the shape of the underlying hazards in the observed data. However, the EAG notes that whilst cure may be expected for some ipilimumab-treated patients, the short follow-up duration in da Silva *et al.* presents challenges for generating plausible long-term extrapolations of PFS and OS based on models directly fitted to these data alone.

(c) Statistical and visual goodness-of-fit

The company's model selection process included consideration of statistical goodness-of-fit (AIC and BIC) and visual inspection. The EAG notes the following observations for each endpoint and each treatment group:

- *Lifileucel PFS* (Table 31 and Figure 17). The company selected the log-normal MCM for inclusion in the base case analysis. This is the second-best fitting MCM based on AIC and BIC. The log-normal model provides a generally good visual fit to the observed data, although all of the MCMs for PFS provide similar predictions over the observed period of Study C-144-01.[28]
- *Lifileucel OS* (Table 33 and Figure 21). The company selected the exponential MCM for inclusion in the base case analysis. This is the best fitting MCM based on AIC and BIC. The exponential MCM provides a generally reasonable visual fit to the observed data, although all of the MCMs for OS provide similar predictions over the observed period of Study C-144-01.[28]
- *Ipilimumab PFS* (Table 31 and Figure 18). The company selected the log-logistic distribution for inclusion in the base case analysis. This is the best fitting distribution based on AIC and BIC. The log-logistic model and all of the standard parametric models for PFS provide a poor visual fit to the observed data over the observed period of da Silva *et al.*[52]

- Ipilimumab OS (Table 33 and Figure 24). The company selected the log-normal distribution for inclusion in the base case analysis. This is the best fitting distribution based on AIC and BIC. The log-normal model and all of the standard parametric models for OS provide a generally reasonable visual fit to the observed data over the observed period of da Silva *et al.*[52]
- Chemotherapy PFS (Table 31 and Figure 19). The company selected the log-logistic distribution for inclusion in the base case analysis. This is the best fitting distribution based on AIC and BIC. The log-logistic model and all of the standard parametric models for PFS provide a poor visual fit to the observed data over the observed period of Mangin *et al.*[30]
- Chemotherapy OS (Table 33 and Figure 25). The company selected the log-normal distribution for inclusion in the base case analysis. This is the best fitting distribution based on AIC and BIC. The log-normal model and all of the standard parametric models for OS provide a generally reasonable visual fit to the observed data over the observed period of Mangin *et al.*[30]

(d) Consideration of nature of hazards

The CS[1] only provides plots comparing the smoothed empirical hazard and the model-predicted hazard for the log-logistic MCM for PFS for lifileucel and for the exponential MCM for OS for lifileucel. Following a request for additional analyses from the EAG (see clarification response,[27] questions B4 and B5), the company provided plots of the smoothed empirical hazards and the model-predicted hazards for: (i) all MCMs for PFS and OS for lifileucel (Figure 35 and Figure 36); (ii) all standard parametric models for PFS and OS for ipilimumab (Figure 37 and Figure 38) and (iii) all standard parametric models for PFS and OS for chemotherapy (Figure 39 and Figure 40).

Figure 35 shows the smoothed empirical versus model-predicted hazards for PFS in the lifileucel group. The smoothed empirical hazard for PFS observed in Study C-144-01[28] increased initially, peaking at ~4 months after the lifileucel infusion, and then dropped markedly thereafter, with the hazard subsequently slowing over time. This pattern is broadly consistent with the model-predicted hazard function for the log-normal MCM for PFS applied in the company's base case model, as well as the log-logistic MCM for PFS used in the company's scenario analyses. The exponential MCM used in the company's scenario analyses does not predict an initial increase in the hazard function up to 4 months after the lifileucel infusion.

Figure 35: Comparison of smoothed empirical and model-predicted hazards, PFS, lifileucel MCMs (reproduced from clarification response, question B4)

Exponential MCM

Weibull MCM

Gompertz MCM

Log-logistic MCM

Log-normal MCM

Generalised gamma MCM

Model did not converge

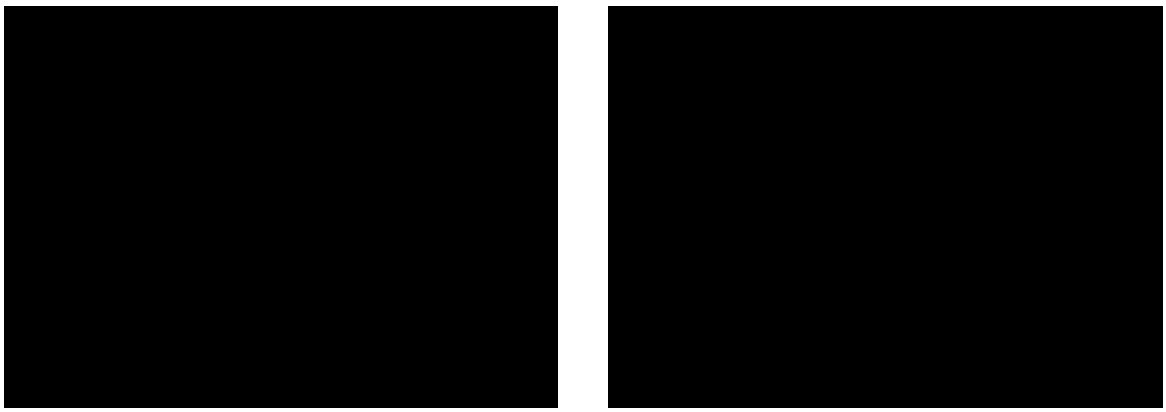
Figure 36 shows the smoothed empirical versus model-predicted hazards for OS in the lifileucel group. The smoothed empirical hazard for OS observed in Study C-144-01[28] decreased steadily over time, and appears to be approaching general OS hazards towards the end of the observed period. This pattern is broadly consistent with the model-predicted hazard function for the exponential MCM for OS applied in the company's base case model. The log-logistic MCM used in the company's scenario analyses is also broadly consistent with this pattern, but initially predicts a hazard of zero and so there is a sharp

increase where the model-predicted hazard increases quickly to meet the smoothed empirical hazard. The EAG notes that the initial value of the smoothed empirical hazard at time zero is dependent upon the smoothing bandwidth and so it should be interpreted with caution in the interpretation of all of the hazard plots.

Figure 36: Comparison of smoothed empirical and model-predicted hazards, OS, lifileucel MCMs (reproduced from clarification response, question B4)

Exponential MCM **Weibull MCM**

Gompertz MCM **Log-logistic MCM**



Log-normal MCM **Generalised gamma MCM**

Figure 37 shows the smoothed empirical versus model-predicted hazards for PFS in the ipilimumab group. The smoothed empirical hazard for PFS observed in da Silva *et al.*[52] generally decreased up to

~10 months after the start of treatment, and then increased thereafter, with the hazard subsequently increasing over time. This pattern is not consistent with the model-predicted hazard function for the log-logistic distribution for PFS applied in the company's base case model; indeed, none of the standard parametric models fitted to the ipilimumab PFS data are reflective of the observed hazard.

Figure 37: Comparison of smoothed empirical and model-predicted hazards, PFS, ipilimumab. standard parametric models (reproduced from clarification response, question B5)

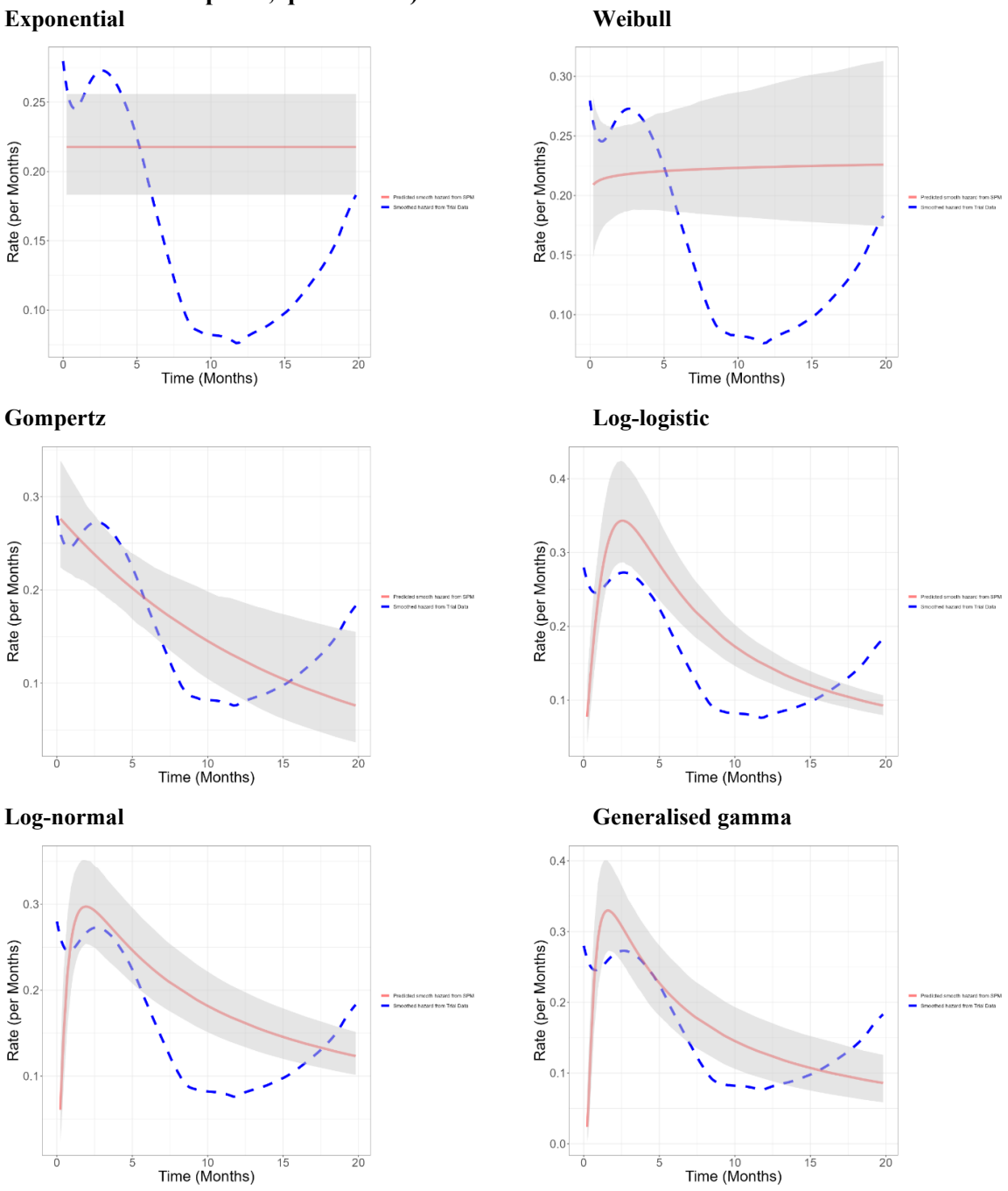
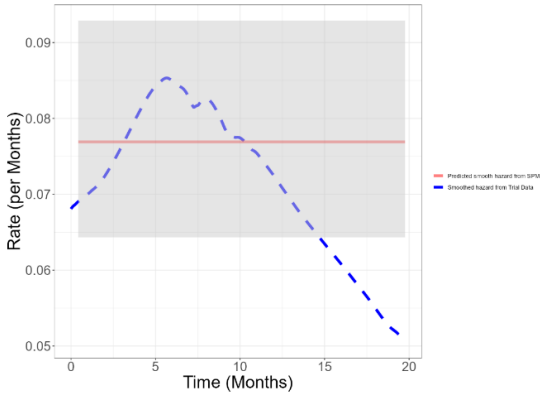


Figure 38 shows the smoothed empirical versus model-predicted hazards for OS in the ipilimumab group. The smoothed empirical hazard for OS observed in da Silva *et al.*[52] increased initially, peaking

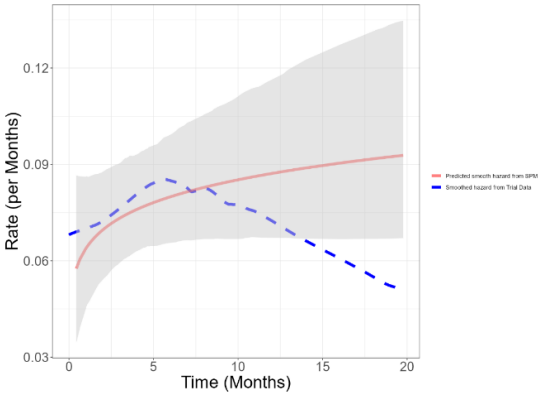
at ~6 months after the start of treatment, and then decreased thereafter, with the hazard subsequently decreasing over time. The general shape of this pattern is compatible with the model-predicted hazard function for the log-normal distribution for OS applied in the company's base case model, as well as the log-logistic distribution for OS used in the company's scenario analyses. However, both distributions predict a sharper initial increase and earlier peak in the hazard function than that seen in the smoothed empirical hazard.

Figure 38: Comparison of smoothed empirical and model-predicted hazards, OS, ipilimumab, standard parametric models (reproduced from clarification response, question B5)

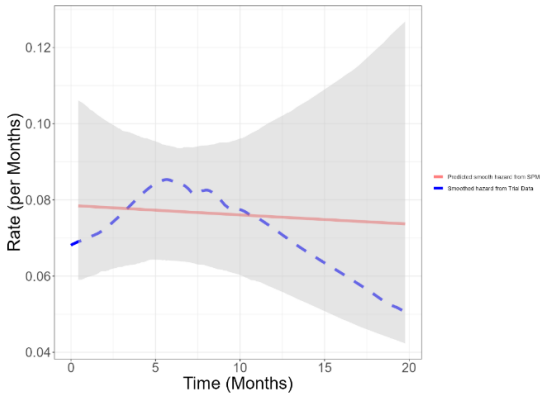
Exponential



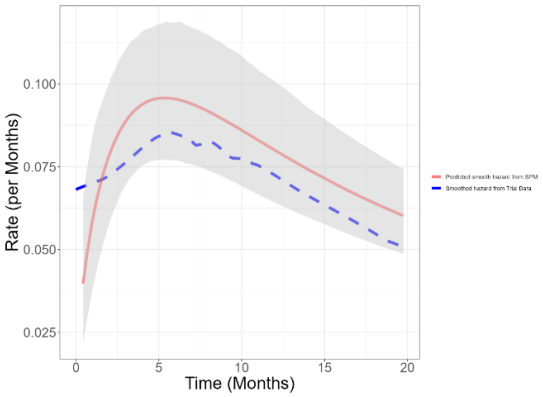
Weibull



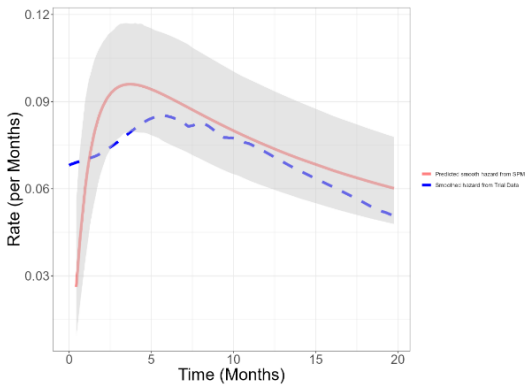
Gompertz



Log-logistic



Log-normal



Generalised gamma

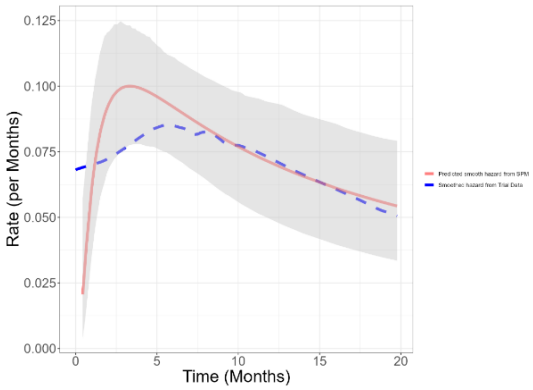
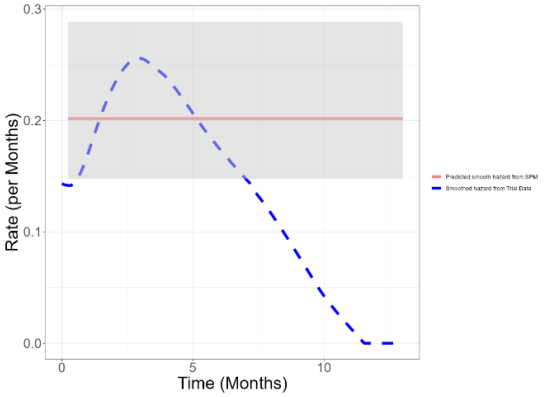


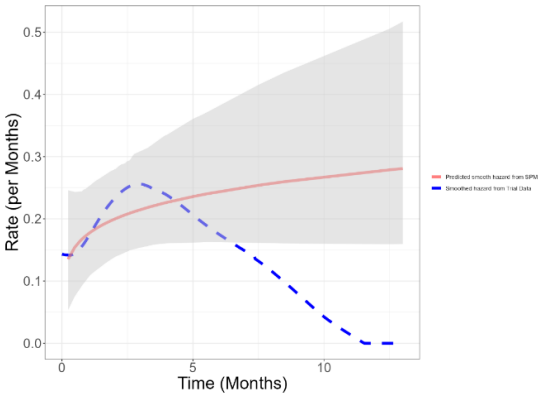
Figure 39 shows the smoothed empirical versus model-predicted hazards for PFS in the chemotherapy group. The smoothed empirical hazard for PFS observed in Mangin *et al.*[30] increased initially up to ~3 months after the start of chemotherapy, and then decreased steadily thereafter, with the hazard approaching zero at ~11 months after the start of chemotherapy. This pattern is weakly compatible with the model-predicted hazard function for the log-logistic distribution for PFS applied in the company's base case model. However, the log-logistic distribution predicts a greater initial increase in the hazard function and the hazard remains greater over time than that seen in the smoothed empirical hazard.

Figure 39: Comparison of smoothed empirical and model-predicted hazards, PFS, chemotherapy, standard parametric models (reproduced from clarification response, question B5)

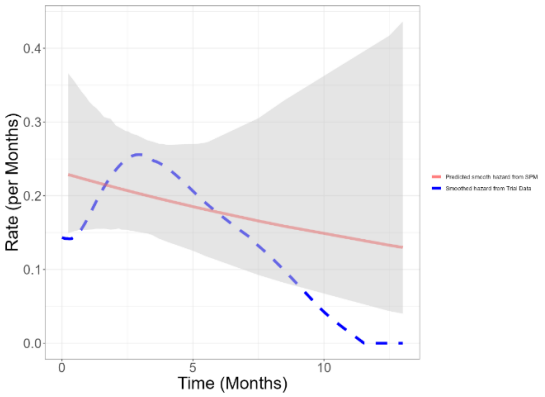
Exponential



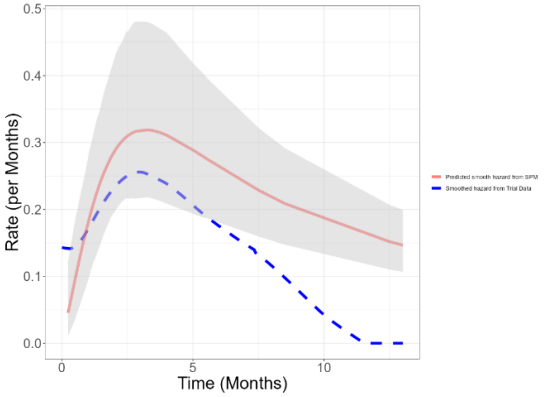
Weibull



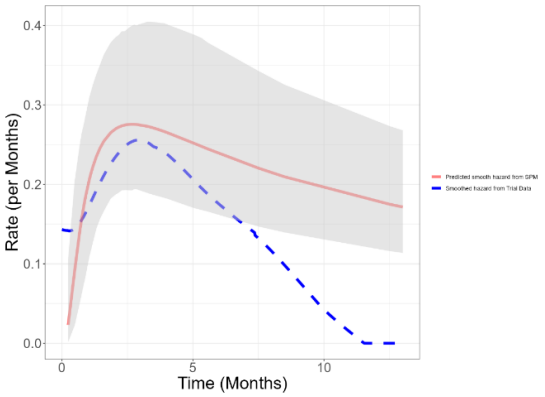
Gompertz



Log-logistic



Log-normal



Generalised gamma

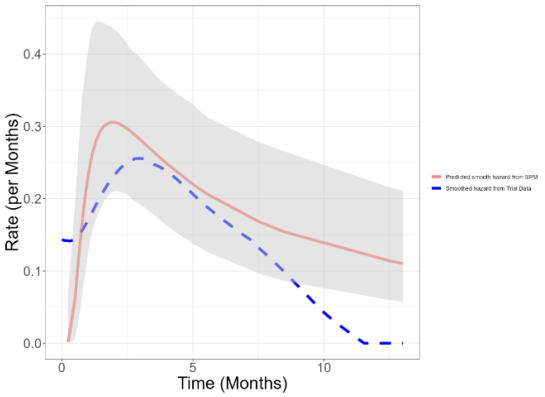
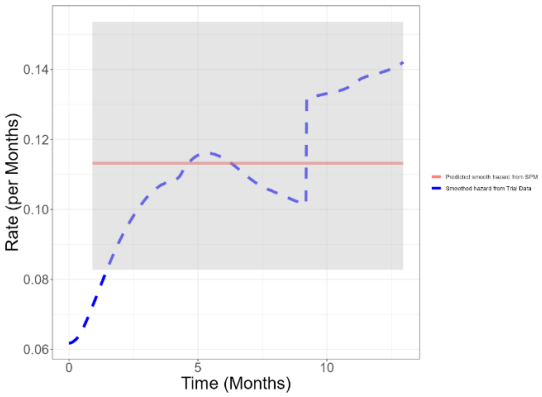


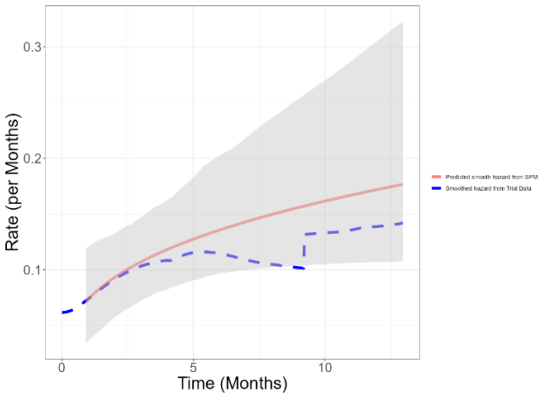
Figure 40 shows the smoothed empirical versus model-predicted hazards for OS in the chemotherapy group. The smoothed empirical hazard for OS observed in Mangin *et al.*[30] generally increased steadily over time, and then decreased steadily thereafter, with the exception of a dip between 6 and 9 months after the start of chemotherapy. The general upward trend in the smoothed empirical hazard is not consistent with the model-predicted hazard function for the log-normal distribution for OS applied in the company's base case model which predicts a peak in the hazard function at ~3 months.

Figure 40: Comparison of smoothed empirical and model-predicted hazards, OS, chemotherapy, standard parametric models (reproduced from clarification response, question B5)

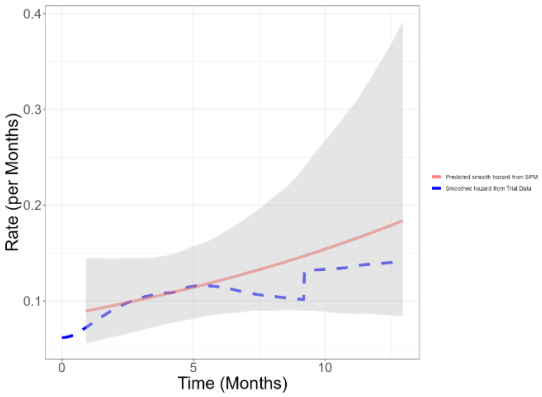
Exponential



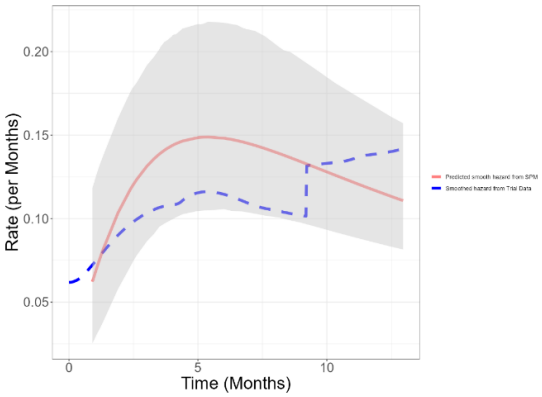
Weibull



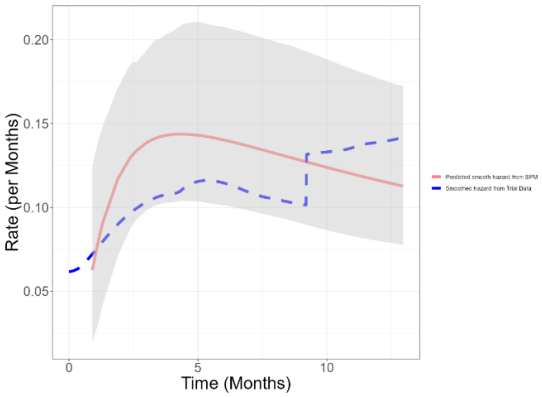
Gompertz



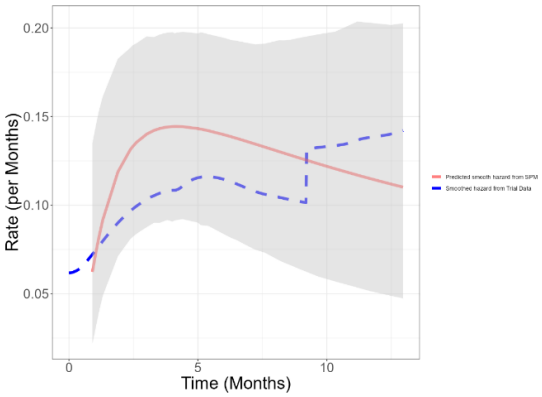
Log-logistic



Log-normal



Generalised gamma



(e) Consideration of long-term clinical plausibility and cure assumption

The CS[1] contains information on the range of expectations of PFS and OS provided by five UK clinical experts consulted by the company at an advisory board meeting. Further information on the views of the consulted clinical experts was also provided in the UK NICE lifileucel advisory board meeting report[26] as well as in the minutes from one-to-one meetings with two clinical experts.[70] The EAG notes three limitations which are discussed below.

(i) Only fitting standard parametric models to the ipilimumab group

The clinical advisors consulted by the company and the EAG indicated that they would expect a proportion of ipilimumab-treated patients to experience long-term survival which may be equivalent to cure. None of the standard parametric survival models fitted to the ipilimumab PFS and OS data are able to reflect a plateau that might be expected had patients in the da Silva study been followed up for longer. Whilst the company's model does attempt to apply a structural cure assumption on OS at 3 years, the model predicts that most patients will have progressed by this point and progression risk is assumed to continue indefinitely despite cure being assumed for OS. As noted above, the absence of longer-term follow-up in da Silva means that there is no obvious means of reflecting potential cure by directly fitting survival models to these data alone.

(ii) Selection of the log-normal MCM for PFS in the lifileucel group

The CS[1] states that the log-normal MCM was selected for inclusion in the base case model for lifileucel PFS based on clinical feedback from one-to-one meetings with two clinical experts. However, the EAG notes that the minutes of these meetings indicate that one clinician expressed no preference, whilst the other clinician preferred the log-logistic MCM. Given that the log-logistic and log-normal MCMs each have a comparable fit (within 3 AIC and BIC points) and predict a similar change in the hazard over time (see Figure 35), the EAG believes that the log-logistic MCM should be included in the base case model for lifileucel PFS, and the log-normal MCM should be used in the scenario analyses.

(iii) Selection of the exponential MCM for OS in the lifileucel group

The CS[1] states that the exponential MCM was selected for inclusion in the base case model for lifileucel PFS based on clinical feedback from one-to-one meetings with two clinical experts. However, the EAG notes that the exponential MCM predicts a cure fraction of [redacted]. The minutes of the one-to-one meetings indicate that one clinician believed that this cure fraction was *"too high"* and that [redacted] would be more plausible, noting that *"in this line of treatment there is little difference between PFS and OS in terms of cure fraction."* One clinician suggested using the same distributional form for both lifileucel PFS and OS. Given that the log-logistic MCM offers a comparable fit (around 3 AIC and BIC points) and has a cure fraction of [redacted], which better aligns with UK clinical expectation, the EAG believes that the log-logistic MCM should be included in the base case model for lifileucel OS.

(f) Sensitivity analysis conducted by the company

The CS[1] includes six scenario analyses around the choice of parametric survival functions (see Table 46). Given that the MCMs appear to fit the lifileucel data well but the standard parametric models do not fit the comparator group data particularly well, it would have been useful to explore the impact of a wider set of survival model choices on the ICERs for lifileucel.

Conclusions on the company's survival analysis

Overall, the EAG considers the company's survival analysis to be reasonable with respect to the analyses presented, but highlight the following issues:

(i) Several of the standard parametric survival models fitted to the data for chemotherapy and ipilimumab do not provide a good representation of the hazards. Alternative more flexible models may have provided a better fit.

(ii) The EAG prefers the use of the log-logistic MCM rather than the log-normal MCM for lifileucel PFS because it is the best-fitting distribution and it aligns with the preferences of clinical experts consulted in the one-to-one meetings held by the company.[70]

(iii) The EAG prefers the use of the log-logistic MCM rather than the exponential MCM for OS in the lifileucel group because it most closely aligns with the cure expectation of [redacted] given by clinicians at the company's advisory board meting[26] and applying this alternative OS model reduces the difference between the PFS and OS cure fraction estimates from [redacted] (in the company base case) to [redacted], which the EAG considers to be more clinically plausible.

(iv) The EAG believes that long-term survival in the ipilimumab group is likely to have been underestimated, with none of the fitted models aligning with clinical expectations of cure for some patients.

(4) Uncertainty around outcomes for cured patients

In the model, patients who are considered cured in the MCMs for lifileucel and patients who are progression-free at 3 years in the ipilimumab group are considered fully cured and incur the same risk of death as the age and sex-matched UK population (SMR =1.0). These patients are also assumed to incur the same health utility as the age and sex-matched general population. The EAG believes that these assumptions are optimistic, and that the cumulative burden of toxicity of previously received treatments would likely affect both survival and HRQoL. The EAG's clinical advisors suggested that the SMR would be slightly higher than 1.0. However, the EAG believes that there is uncertainty around which SMR estimate would be most appropriate for use in the model.

The CS[1] presents a scenario analysis using an SMR of 1.57 from Moke *et al.*[114] for all causes of death in melanoma survivors from a population-based study with adolescents and young adults (aged 15–39 years at diagnosis) utilising Surveillance, Epidemiology, and End Results (SEER) registry data from

the US. Applying this higher SMR increases the ICER in the original model from [redacted] to [redacted] in the comparison against ipilimumab, from [redacted] to [redacted] in the comparison against chemotherapy, and from [redacted] to [redacted] in the comparison against BSC.

The EAG notes that changing the SMR value alone, without changing the assumption of cure at 3 years, has a limited impact on the ICER. Changing the cure timepoint to 5 years and applying an SMR of 1.57 increases the ICERs for lifileucel versus all comparators by around £5,000.

(5) Uncertainty around outcomes for patients who do not receive the lifileucel infusion

The company's model assumes that amongst the population of patients in whom the lifileucel infusion is planned, [redacted] will not receive the infusion. These patients are assumed to receive one of the model comparators, with costs and outcomes based on a weighted average of the model comparator groups (ipilimumab [redacted], chemotherapy [redacted] or BSC [redacted]). The EAG notes that the CS[1] does not contain any information on the observed survival outcomes for patients in Study C-144-01[28] who did not receive the infusion. Therefore, the appropriateness of these assumptions is unclear. During the clarification process, the EAG asked the company to provide Kaplan-Meier plots of PFS and OS for people in Cohorts 2 and 4 of Study C-144-01 who did not receive the infusion (see clarification response,[27] question A21). In their response, the company stated: *"Creating these plots would require additional processing of patient-level data, internal reviews and obtaining additional internal approvals before they are shared with external parties. Therefore, unfortunately, the Company will not be able provide these plots feasible within the timeframe provided for the clarification questions."*

As such, the EAG is unsure whether the modelled outcomes and costs for patients who do not receive the lifileucel infusion reflect what was observed for non-infused patients in Study C-144-01.[28] The EAG is also unsure whether these data will be made available within the overall timescales for the appraisal.

(6) Uncertainty around assumed relative treatment effect for BSC versus chemotherapy

As noted in Section 4.4, the company was unable to identify any published evidence on outcomes for patients with metastatic melanoma who receive BSC alone. The minutes of the company's advisory board meeting[26] state that: *"KOLs (key opinion leaders) were in agreement that it was significantly inferior to chemotherapy, and structured elicitation resulted in agreement that it could be represented by a curve that was 50% worse than the chemotherapy response curve and progression curve (chemotherapy curves presented from Mangin et al.)."* Based on this structured elicitation exercise, the company's model applies an HR of 2.0 to the selected parametric survival models for PFS and OS for the chemotherapy group to derive these outcomes for BSC.

The EAG acknowledges the lack of published evidence to inform outcomes for BSC but notes the following concerns:

- The minutes of the company's advisory board meeting[26] state that *"some KOLs said that chemotherapy was about the same as giving no treatment (i.e., no treatment effect)."* This view contrasts with the assumed HR applied in the company's base case model.
- It is unclear what questions were asked during the company's structured elicitation exercise and how potentially conflicting views of clinicians were accounted for.
- The EAG's clinical advisors stated that they would expect outcomes for BSC to be similar to those for chemotherapy.
- Owing to the lack of evidence, outcomes for BSC should be considered highly uncertain. However, this HR is fixed in the company's PSA and it has not been explored in the company's scenario analyses.

As part of the clarification process, the EAG asked the company to clarify how many clinical experts attending the advisory board meeting shared the view that chemotherapy provides no advantage over BSC and to explain why an HR of 1.0 is not applied in the model (see clarification response,[27] question A34). The company's response reiterates the same information provided in the CS[1] and does not provide any additional information on the number of experts attending the advisory board meeting who believed that chemotherapy provides no additional benefit.

The EAG's preferred analysis assumes that outcomes for BSC and chemotherapy are equivalent in terms of PFS and OS (HR=1.0), based on the views of the EAG's clinical advisors and an unspecified number of clinical experts who attended the company's advisory board meeting who also shared this view. The company's base case assumption (BSC vs chemotherapy HR = 2.0) is tested as part of the EAG's additional sensitivity analyses (ASAs).

(7) Issues relating to utility values

(a) Issues related to health state utility values

The utility values applied to the PF and PD health states are based on unweighted means of utility values reported in 2 published studies and 10 TAs (see Section 5.2.4). The EAG considers this unweighted averaging approach to be unconventional – it is more typical for utility values to be taken from the same clinical study used to inform effectiveness outcomes in the model, or from some individual external source which is judged to be relevant and applicable to the health states included in the model. The EAG also notes that some of the utility values included in the unweighted average do not relate to patients at the relevant lines of therapy for the lifileucel target population (2L, or 3L if BRAF+) and some utility values should not be included as they do not reflect EQ-5D-3L values and therefore they do not adhere to the NICE Reference Case.[109]

In response to clarification question B12,[27] the company justified their unweighted mean approach as being consistent with the approach taken in NG14,[14] stating that all utility values in the selected NICE TAs were derived from relevant clinical trials, and that selecting one single source could introduce bias. With respect to the assumption that PD utility values from models of 1L treatments are equivalent to PF utility values for 2L treatment, the company's response states that this approach was *"based on the rationale that patients who progress from first-line treatment would experience a similar quality of life when receiving second-line treatment."* The company's response also acknowledges that including non-EQ-5D-3L utility values is a limitation, but states that this approach was adopted *"to ensure that all relevant and available data were considered in the analysis."*[27] The EAG remains unclear whether the utility values applied to PD states in earlier 1L models would be applicable to patients receiving 2L lifileucel or its comparators.

The CS[1] (Section 3.4.4) states that the clinical experts who attended the clinical advisory board were shown the utility values reported by Retel *et al.* (PF utility = 0.85, PD utility = 0.59) and they *"expected a larger gap between PF and PD utility values, with a higher PF utility value."* The EAG notes that amongst the sources included in the company's HRQoL review (see Table 38), Retel *et al.* reports the largest difference between the PF and PD values and the highest PF value; however, preferences were elicited using a standard gamble approach rather than the EQ-5D-3L. The company's clarification response[27] includes an additional scenario analysis whereby non-EQ-5D values (Retel *et al.*,[61] TA269[15] and TA319)[16] were excluded from the unweighted mean utility values (resulting utility values: PF = 0.76, PD = 0.70). The impact on the ICERs for lifileucel was fairly small (<£1,000 per QALY). The company did not present any additional scenario analyses to test the impact of removing TAs of 1L therapies as sources of utility values for the PD state. However, the CS does include scenario analyses which apply utility values from one single source: Retel *et al.* (PF utility = 0.85; PD utility = 0.59) and TA357 (PF utility = 0.74, PD utility = 0.69). Within these scenarios, the impacts on the ICERs for lifileucel are also relatively small (<£1,500 per QALY). The EAG notes that the 3-year cure assumption limits the impact of the magnitude of the PF state utility value.

Overall, the EAG believes that there is no single source which provides utility values which are both clinically plausible and which adhere to the NICE Reference Case. The EAG's preferred analyses retains the company's base case estimates; however, the EAG considers that these estimates should be approached with caution. Sensitivity analyses are considered using the highest reported PF value and the lowest reported PD value from the EQ-5D-3L analyses included in the company's HRQoL review.

(b) Concerns regarding QALY loss associated with lifileucel administration

The model applies a disutility of -0.09 associated with the lifileucel administration based on values reported by Sung *et al.*[73] and Kelly *et al.*[74] (see Section 5.2.4.4). Neither study used the EQ-5D-3L and

neither reflects an adult melanoma population. The EAG in TA975[99] reported that the former is based on a visual analogue scale (VAS) completed by 12 physicians who care for patients undergoing bone marrow transplantation, whilst the latter is derived from adjusted Short Form-36 (SF-36) scores from the Swiss Childhood Cancer Survivor Study and was mapped to the Health Utilities Index Mark 2 (HUI-2). The company's clarification response[27] (question B14) acknowledges these limitations, but justifies the use of Kelly *et al.* given the absence of data directly applicable for lifileucel *"as part of a proxy to calculate the relative disutility associated with lifileucel administration, rather than as an absolute utility input."* The company also stated that the disutility value from Sung *et al.* was used in TA975 to reflect the impact of CAR-T therapy on HRQoL, which is considered more invasive than lifileucel, and that the resulting ratio obtained from the two values is intended to reflect the *"temporary disutility associated with lifileucel administration in the PF state"* and it provides a pragmatic approach in the absence of lifileucel-specific utility data. The EAG remains unclear whether these estimates are relevant to the target population for the current appraisal.

The EAG notes that the lifileucel administration-related disutility is applied only to the 20% of patients receiving lifileucel who are assumed to require an ICU stay. The company's clarification response[27] (question B14) justifies this assumption based on the clinical experts' view that *"most patients are anticipated to experience mild, transient symptoms with limited impact on QoL"* and *"approximately 20%, are expected to require ICU admission, primarily in relation to IL-2 administration."* Therefore, the company argues that this approach avoids overestimating the impact of lifileucel administration on HRQoL. Overall, the EAG is unsure whether the net QALY loss adequately reflects the negative impact of lifileucel administration experienced by infused patients in Study C-144-01.[28] It is also unclear whether some of this negative impact may already be reflected in the AE-related QALY losses which are already considered elsewhere in the model. This issue is included in the EAG's exploratory analyses (see Section 5.5).

(8) Issues relating to costs

(a) Costs of tumour tissue resection

The company's estimate for the costs of the tumour tissue procurement, which form part of the costs of the overall lifileucel regimen, correspond to a weighted mean cost obtained using codes from NHS Reference Costs 2023/24[75] for different resection sites (lung, lymph node, liver, musculoskeletal, skin/subcutaneous, breast, and peritoneal/retroperitoneal). These unit costs are weighted initially by the corresponding activity for each code,[75] and then weighted a second time using the proportion of tumour resections at each resection site from Study C-144-01.[28] The EAG believes that the costs of the tumour resection should be weighted only by the data on the distribution of resection sites of patients receiving lifileucel from Study C-144-01,[28] rather than reflecting all NHS activity (see critical appraisal point 1(h)). This issue is explored in the EAG exploratory analysis in Section 5.5.

(b) Cost of implementation, logistics, training and delivery related to lifileucel

As reported in Section 5.2.4.5, the costs of administering the lifileucel infusion include one day of inpatient stay (£535.33) based on inpatient day cases related to skin disorders from NHS Reference Costs 2023/24.[75] Other administration costs related to the lifileucel regimen include [redacted] days of hospital stay for tumour tissue procurement, [redacted] days of inpatient stay for LD chemotherapy, [redacted] day for the lifileucel infusion and 10 days of hospitalisation (in ICU and a general ward) during the IL-2 regimen and following it for monitoring purposes. The total administration costs (excluding the costs of the tumour procurement) are estimated to be [redacted] for patients who receive the within-specification lifileucel infusion. Other costs associated with set-up, training and logistics are not included in the model.

The company's clarification response[27] (question B16) states that *"hospitals already offering cell therapy should have staffing and internal processes in place"* and that the company *"provides a robust onboarding process and substantial ongoing operational support for no extra charge."* The company also states that costs related to logistics support, training and operational support *"are not warranted to be included."* The EAG has concerns that the introduction and delivery of lifileucel in the NHS may lead to other costs which have not been captured in the administration costs reflected in the company's model. The EAG is aware that NHSE has developed a specific tariff for CAR-T therapies which includes the costs of *"leukapheresis, delivery of the CAR-T in hospital, AEs occurring in hospital, monitoring for 100 days and training."*

The EAG sought clarification from NHS England about whether the CAR-T tariff should be applied as part of the costs of the lifileucel regimen. NHS England clarified that that the 2025/26 CAR-T tariff should be included in the model, at a cost of [redacted]. NHS England explained that it [redacted] The NHS England CAR-T tariff is included in the EAG's preferred analysis (see Section 5.5).

(c) Costs of lifileucel premedication

The draft SmPC for lifileucel[12] states that patients should receive *"paracetamol and diphenhydramine or another H1-antihistamine, approximately 30 to 60 minutes prior to AMTAGVI infusion."* These costs

are not included in the company's model; however, as these drugs are inexpensive their exclusion is expected to have only a minor impact on the ICERs.

(d) Costs of chemotherapy

The acquisition and administration costs for chemotherapy are based on the assumption that 65% of patients receiving chemotherapy would receive dacarbazine monotherapy, and the remaining patients would receive temozolomide monotherapy, carboplatin in combination with paclitaxel, dacarbazine in combination with cisplatin, or carboplatin monotherapy.[1] Both of the EAG's clinical advisors stated that in clinical practice in England, amongst the small proportion of patients with previously treated advanced melanoma who would receive chemotherapy, the vast majority would receive dacarbazine. The EAG explores the use of only dacarbazine as the chemotherapy regimen in the EAG exploratory analyses in Section 5.5.

(9) Inappropriate use of a higher decision modifier for ipilimumab

The company's model applies decision modifier of 1.7 for all economic comparisons; this is reflected in all of the cost-effectiveness results presented in the CS.[1] Based on the York Shortfall Calculator,[108] the characteristics of patients in the PDAwCS efficacy set of Study C-144-01 (age = [redacted] years and [redacted] female)[28] and the model-predicted QALY gains for each comparator, the decision modifier for the comparison of lifileucel versus ipilimumab is 1.2, whereas the decision modifier for the comparisons of lifileucel versus chemotherapy and BSC is 1.7 (see Table 49).

Table 49: Absolute and proportional shortfall estimates for all lifileucel comparators based on York Shortfall Calculator

Comparator	Mean QALYs for comparator	Absolute shortfall	Proportional shortfall	Decision 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

QALY - quality-adjusted life year; BSC - best supportive care

Regardless of the different weightings for ipilimumab, chemotherapy and BSC indicated in Table 49, the CS[1] argues that a decision modifier of 1.7 should apply to all comparators to lifileucel based on the following arguments:

- The proportional shortfall (PS) for ipilimumab is *"remarkably close"* to the 95% PS threshold required for lifileucel to qualify for a higher decision modifier of 1.7.
- When accounting for the estimated usage of all comparators in NHS practice (ipilimumab [redacted]; chemotherapy [redacted]; BSC [redacted]), lifileucel would qualify for an overall decision modifier of 1.7.

- Lifileucel would have qualified for NICE's previous End of Life (EoL) criteria, as described in the 2013 NICE Methods Guide.[115] EoL criteria were met in several previous TAs of treatments for metastatic melanoma (including TA366,[19] TA384[66] and TA396[20]).
- Whilst NICE's previous EoL criteria were met in several NICE TAs, many of these technologies would not qualify for a decision modifier above 1.0 based on the severity weighting approach. The CS states that there is an equality argument of *"lifileucel (and melanoma patients) being disadvantaged by the paradigm shift from end-of-life modifier to the severity modifier."*
- The modelled QALY gains for the ipilimumab comparator group are optimistic as they include a *"conservative assumption for long-term survival of ipilimumab patients."*[1] Whilst unclear from the CS, the EAG believes that this point refers to the company's model assumption that ipilimumab-treated patients who remain alive and progression-free at 3 years are cured for OS.

The EAG agrees with the company that a decision modifier of 1.7 should apply to the chemotherapy and BSC comparators. However, the EAG disagrees that this higher decision modifier should also apply to ipilimumab for the following reasons:

- The EAG takes the general view that the relevant decision modifier should be based on estimates of absolute shortfall (AS) and PS derived from the comparator QALYs in the economic model. The company's model-predicted QALYs indicate that a decision modifier of 1.2 should be applied for the comparison against ipilimumab. The EAG notes that the "tipping point" at which ipilimumab would warrant a decision modifier of 1.7 is 0.71 QALYs for ipilimumab, whereas the company's modelled estimate is higher at 0.88 QALYs.
- NICE DSU TSD 23[116] states that: *"Where multiple comparators are presented and all represent practices that occur to some degree within the NHS, estimates of AS and PS should be presented for each. It is committee judgement that should determine which is the most appropriate comparator as is currently undertaken when interpreting cost effectiveness results."* The TSD explains that the decision modifier should be determined for each individual comparator to lifileucel, rather than based on a basket of comparators. Given that the company's model estimates pairwise ICERs for lifileucel against each individual comparator, determining the severity modifier on the basis of a blended comparator would introduce an inconsistency between the approaches used to estimate the ICERs and the relevant decision modifiers.
- The company's arguments around EoL criteria are not relevant to the current appraisal as these criteria do not reflect NICE's current decision-making approach based on disease severity.[109]
- In contrast to the company's view, the EAG considers the company's survival estimates for ipilimumab are likely to be underestimated as they do not fully reflect expectations of cure for any patients (see critical appraisal point 3). The EAG's preferred analyses include more optimistic

estimates of survival for ipilimumab which indicate that the relevant decision modifier for the comparison against ipilimumab should be 1.2.

On the basis of the above concerns, the EAG's preferred analysis applies a decision modifier of 1.2 for ipilimumab and a decision modifier of 1.7 for chemotherapy and BSC.

(10) Poor implementation of PSA

Table 50 summarises the distributions applied in the company's PSA. The EAG's concerns regarding the distributions used in the PSA are detailed below.

Table 50: Distributions applied in the company's PSA

Parameter group	Distribution
Patient characteristics	Age – gamma % male – beta Weight – gamma BMI – gamma Creatinine clearance – fixed BSA – fixed eGFR – fixed
Lifileucel decision tree probabilities	Beta, although some parameters are held fixed
Parametric survival models	Multivariate normal
SMR	Fixed
Health state utility values	Beta
General population utility values	Fixed
AE disutility values	Beta
Lifileucel administration disutility	Beta
AE frequencies	Not modelled directly
Distribution of comparator therapies received if lifileucel is not infused	Fixed
Distribution of chemotherapy regimens in basket	Dirichlet
Ratio of HRs applied in STC adjustment	Uniform
RDI for all drugs	Beta
Length of stay	Fixed
Proportions of patients incurring lifileucel decision tree costs	Beta
Drug acquisition costs	Fixed
Drug administration costs	Gamma
Lifileucel regimen administration costs	Gamma
Health state costs (PF and PD)	Gamma
AE costs	Gamma
End-of-life care costs	Gamma

AE - adverse event; BMI - body mass index; BSA - body surface area; eGFR - estimated glomerular filtration rate; HR - hazard ratio; PF - progression-free; PD - progressed disease; PSA - probabilistic sensitivity analysis; RDI - relative dose intensity; SMR - standardised mortality ratio; STC - simulated treatment comparison.

The EAG notes the following limitations in the company's PSA:

- *Fixed parameters:* Several uncertain parameters are purposefully held fixed. This includes some patient characteristics (creatinine clearance, BSA and eGFR), several lifileucel decision tree probabilities, and all probabilities relating to the basket of therapies received if the lifileucel infusion is not received.
- *RDI estimates:* The model applies beta distributions to sample estimates of RDI. All of these parameters have a mean value which is close to 1.0 and each distribution assumes an SE of 20% of the mean. This leads to estimates of alpha and beta which are negative – this results in the beta distribution function returning errors in all samples. The model includes =IFERROR() functions which override these errors and instead applies fixed values. The model should have used observed data to estimate alpha and beta, where possible, and more meaningful SEs where data are not available.
- *Lifileucel decision tree probabilities:* Similar to the problems with RDI, the decision tree probabilities are modelled as beta distributions whereby some parameters have a mean value which is close to 1.0 and an SE of 20% of the mean. Again, this leads to errors which are overridden by =IFERROR() functions which consequently return fixed values in the PSA. These parameters would have been better modelled using Dirichlet distributions based on observed numbers of patients in Study C-144-01.[28]
- *Chemotherapy regimen weighting:* The distribution of alternative chemotherapy regimens is modelled using a Dirichlet distribution. The company's sampling method applies a prior of 0.50 to the probability of receiving each chemotherapy regimen. This is incorrect as the priors should have been applied to the number of patients receiving each regimen rather than the probabilities. The consequence is that the posterior probability of receiving each chemotherapy regimen in the PSA is very different to that applied in the deterministic version of the model.
- *Health state utility values:* The model includes separate parameters for the health state utility values for each treatment (e.g., PF on lifileucel, PF on ipilimumab, PF on chemotherapy etc.) and these are sampled separately using independent distributions. This means that for the same PSA iteration, different utility values are sampled between treatments for the same health state. The EAG believes that these parameters should have been defined as common parameters which are shared across all treatments. In addition, because the utility values for the PF and PD states are sampled independently from one another, the sampled utility value for the PD state is frequently higher than the sampled utility value for the PF state. The model should instead have applied methods to account for the logical ordering of the PF and PD health states. In addition, the sampled utility values for the PF and PD states are not capped by general population EQ-5D; this means that some PFS samples result in higher utility values for patients with advanced melanoma compared with the general population.

- *Health state costs:* Similar to the approach taken to sample utility values, the model includes separate parameters for the health state costs for each treatment and these are sampled using independent distributions. This means that for the same PSA iteration, different costs are sampled between treatments for the same health state.
- *HRs:* The CS[1] states that the STC-adjusted HR and unadjusted HR are sampled from log-normal distributions. However, this description is not accurate. When a log-normal distribution is selected for inclusion in the PSA in the executable model, the selected function is a uniform distribution (defined as =a+(b–a)*RAND()). The EAG believes that the HRs should have been sampled independently using log-normal distributions.

Overall, the EAG believes that the company's PSA provides a weak characterisation of parameter uncertainty.

The EAG highlighted the issue related to the sampling of health state utility values as part of the clarification process (see clarification response,[27] question B21). In its clarification letter, the EAG suggested incorporating an alternative sampling method for handling ordered parameters proposed by Ren *et al.*[117] The other problems discussed above were identified through further model scrutiny which was undertaken after the EAG's clarification letter had been submitted. The company's clarification response states that the Ren method for sampling ordered parameters *"requires a significant amount of time and is not feasible to implement it at this stage."* The company's clarification response also states that as part of its updated model, an alternative sampling approach has been applied whereby the sampled utility value for the PD state is capped by the sampled utility value for the PF state. The EAG notes that the company's updated approach is incorrect as the expected utility value for the PD state across all probabilistic samples no longer reflects its point estimate (PD utility value point estimate = 0.67; mean of PD utility samples capped by sampled PF utility = 0.63). The EAG also disagrees that the implementation of the Ren sampling approach is time-consuming – the supplementary materials to the paper include an executable Excel file which performs the sampling method. The calculations which perform the sampling could have been pasted into the model and linked to the existing utility parameters. However, the EAG notes that resolving the problem of sampling of ordered utility parameters would address only one of several problems in the company's PSA.

The EAG further notes that the ICERs obtained from the probabilistic version of the model are noticeably lower than those generated using the deterministic model (see Section 5.2.6). These differences are driven by the estimates of mean QALYs and costs for the lifileucel group. However, these differences are not a consequence of the issues described above; rather, they appear to be caused by the sampling of the MCMs. The EAG does not believe that there are errors in how the MCMs are

sampled. Overall, the EAG considers the results of the deterministic model to be more reliable than those obtained from the probabilistic model.

(11) Uncertain relevance of non-Reference Case discount rates

The NICE Methods Manual[109] states the following: *"The 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."*

The CS[1] presents an argument in support of using non-Reference Case discount rates of 1.5% for health outcomes and costs. The company's base case analysis uses discount rates of 3.5%; model results including discount rates of 1.5% are presented as part of the company's scenario analyses (see Section 5.2.6). The CS argues that the NICE criteria for non-Reference Case discount rates are met as lifileucel is a one-off cell therapy with high upfront costs which provides long-term health benefits, including curative potential.

The EAG is unsure whether non-Reference Case discount rates are relevant for decision-making. Whilst the EAG's clinical advisors agreed that a proportion of patients who receive the lifileucel infusion are expected to achieve long-term survival and improved HRQoL, these benefits are expected to apply only to a minority of patients for whom the lifileucel infusion is planned. The EAG notes that within the overall population in whom lifileucel treatment is planned, an estimated [redacted] of patients will go on to receive the infusion, and of these, the company's model applies and estimated cure fraction for OS of [redacted] (based on the unadjusted analysis of Study C-144-01[28]). Taken together, the model predicts that around [redacted] of patients in whom lifileucel is planned will achieve cure, and the remaining [redacted] of patients will have poor survival outcomes. The EAG believes that the Appraisal Committee will need to reach a judgement about whether this magnitude of benefit is sufficient to warrant the use of non-Reference Case discount rates.

5.4 Summary of the company's updated economic model

As part of its clarification response,[27] the company provided an updated version of the model which addresses most of the errors and other issues raised in the EAG's clarification letter (see Section 5.3.5, errors (a)-(h). The company's updated base case model includes the following amendments:

- General population mortality risks by age and sex were amended to reflect life tables for UK for the period 2021-2023.[111]

- The model trace and mortality risks calculations and were amended to assume that there are 52.18 weeks per year (changed from 52.00).
- The acquisition and administration costs of ipilimumab were updated to reflect a mean treatment duration of 3.6 cycles and are applied as a lump-sum cost in the first model cycle.
- Costs associated with managing AEs were included for patients who receive an out-of-specification lifileucel infusion.
- Drug costs for dacarbazine were adjusted to reflect 3 treatment days rather than 2.16 treatment days, in line with the drug's dosage schedule. Drug costs for other regimens were also updated to address this issue.
- Drug administration costs for temozolomide were adjusted to account only for one administration cost being applied at start of treatment, rather that applying the administration cost on every day that a patient takes a pill.
- The formulae which calculate the weighted costs of biopsy on musculoskeletal site, as part of the costs of tumour tissue procurement were amended to resolve the error whereby the incorrect weights were used.
- The cost of 'Palliative care physician visit- outpatient', which is part of the health state costs, was amended to include only costs associated with medical specialists (updated unit cost of £243.00).
- The formulae which apply age-adjusted utility were using Hernandez Alava *et al.*[71] were corrected to instead return the EQ-5D-3L estimate for the general population at age [redacted] when the age adjustment function is set to "No" (included in the company's sensitivity analysis where age adjustment is excluded only).
- The formulae in the lifileucel and ipilimumab model traces which calculate the undiscounted QALYs for the cured group in the PF state were amended to return the general population EQ-5D-3L value at age [redacted] years.
- The approach used to sample utility values for the PF and PD states was amended whereby a cap was applied to prevent the sampled PD utility from exceeding the sampled PF utility value in each probabilistic sample.

The results of the company's updated base case model are summarised in Table 51. The company's updated model suggests higher deterministic ICERs compared with the original model (updated ICERs: lifileucel vs ipilimumab = [redacted] per QALY gained; lifileucel versus chemotherapy = [redacted] per QALY gained; lifileucel versus BSC = [redacted] per QALY gained). The updated version of the probabilistic model also suggests higher ICERs compared with the original model. The EAG notes that a small number of additional errors were identified in the company's updated model; these have been corrected as part of the EAG's exploratory analyses (see Section 5.5).

Table 51: Company's base case updated results, lifileucel versus comparators, pairwise

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER (excl. DM)	ICER (incl. DM)
Probabilistic model								
Lifileucel (STC-adjusted) versus ipilimumab (DM=1.7)								
Lifileucel	8.62	4.19	[redacted]	7.28	3.35	[redacted]	[redacted]	[redacted]
Ipilimumab	1.34	0.84		-	-	-	-	-
Lifileucel (unadjusted) versus chemotherapy (DM=1.7)								
Lifileucel	5.82	2.95	[redacted]	5.00	2.39	[redacted]	[redacted]	[redacted]
Chemotherapy	0.82	0.56		-	-	-	-	-
Lifileucel (unadjusted) versus BSC (DM=1.7)								
Lifileucel	5.82	2.95	[redacted]	5.41	2.67	[redacted]	[redacted]	[redacted]
BSC	0.41	0.29		-	-	-	-	-
Deterministic model								
Lifileucel (STC-adjusted) versus ipilimumab (DM=1.7)								
Lifileucel	8.51	4.07	[redacted]	7.19	3.20	[redacted]	[redacted]	[redacted]
Ipilimumab	1.32	0.87		-	-	-	-	-
Lifileucel (unadjusted) versus chemotherapy (DM=1.7)								
Lifileucel	5.78	2.87	[redacted]	4.98	2.31	[redacted]	[redacted]	[redacted]
Chemotherapy	0.79	0.56		-	-	-	-	-
Lifileucel (unadjusted) versus BSC (DM=1.7)								
Lifileucel	5.78	2.87	[redacted]	5.37	2.58	[redacted]	[redacted]	[redacted]
BSC	0.41	0.29		-	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; DM - decision modifier; Inc. - incremental; NR - not reported
** Undiscounted*

5.5 Exploratory and sensitivity analyses undertaken by the EAG

5.5.1 Exploratory analyses methods

The EAG undertook exploratory analyses (EAs) using the updated version of the model which was provided as part of the company's clarification response.[27] Owing to unresolvable problems with the company's PSA, all EAs were undertaken using the deterministic version of the model. All analyses were undertaken by one modeller and checked by a second modeller. All analyses presented in this section reflect the PAS price of lifileucel. Results are presented with and without QALY weighting. The results of the analyses including confidential price discounts for other drugs included in the model are provided in a separate appendix to this report.

EAG's preferred analysis

The EAG's preferred analysis is comprised of 7 sets of amendments to the company's updated model. Each of EAs 1-7 are applied individually.

EA1: Correction of errors

The following further corrections were applied to the company's updated model:

EA1a: General population mortality risks were amended to use life tables for England for the period 2021-2023 (rather than the UK).[111]

EA1b: The general population mortality risk calculations in the model were modified to apply the sex distribution in Study C-144-01[28] from age [redacted] years rather than age 0 years.
EA1c: Estimates of AE frequencies for ipilimumab from da Silva *et al.*[52] were amended to use 2 decimal places (rather than rounding down to integer values). This amendment also resolves the minor discrepancy between the frequency of hypophysitis used by the company and reported da Silva *et al.,* as mentioned in Section 5.3.3.
EA1d: The model was amended to apply the number of patients per resection site in Study C-144-01[28] to estimate the costs of tumour procurement.
EA1e: The decision modifier was amended to reflect the multiplier indicated by the York QALY Shortfall Calculator[108] for each pairwise comparison. This leads to a decision modifier of 1.2 for ipilimumab and 1.7 for chemotherapy and BSC.

These model corrections are included in all subsequent exploratory analyses.

EA2: Application of inverse STC-adjusted HR to unadjusted lifileucel PFS and OS MCMs to estimate outcomes for ipilimumab group

This analysis includes two changes to the company's model:

(i) The ratio of the STC-adjusted and unadjusted HRs for lifileucel versus ipilimumab was set equal to 1.0 (i.e., the lifileucel MCMs reflect the unadjusted models)
(ii) The inverse STC-adjusted HR for lifileucel versus ipilimumab was applied to the unadjusted lifileucel MCMs for PFS and OS to estimate outcomes for the ipilimumab group.

The application of this alternative approach means that all economic comparisons reflect the outcomes for lifileucel observed in Study C-144-01,[28] thereby reflecting outcomes for the target population, rather than the da Silva *et al.*[52] ipilimumab population. Because the EAG's analysis applies an HR to the lifileucel MCM, this approach also results in a plateau in model-predicted PFS and OS for the ipilimumab, thereby indicating outcomes similar to cure for a small proportion of ipilimumab-treated patients. This is more consistent with the clinical opinion obtained by the company and the EAG regarding the potential for long-term PFS and OS in ipilimumab-treated patients (see Figure 41).

Figure 41: Alternative estimates of PFS and OS based on inverse HRs applied to the lifileucel MCMs as a baseline

PFS - progression-free survival; OS - overall survival; STC - simulated treatment comparison; HR - hazard ratio; KM - Kaplan-Meier; EAG - External Assessment Group

EA3: Application of HR for BSC versus chemotherapy of 1.0

Based on clinical opinion obtained by the EAG, the HR for BSC versus chemotherapy was assumed to be equal to 1.0 (i.e., no additional treatment effect over BSC).

EA4: Use of log-logistic MCMs for PFS and OS

Based on the goodness-of-fit of the fitted distributions and clinical expectations of cure, the model was amended to use log-logistic MCMs for PFS and OS in lifileucel-infused patients.

EA5: Cure time point = 5 years

Based on clinical opinion obtained by the EAG, the cure time point was set equal to 5 years. This parameter influences the duration of clinical follow-up and the time point at which HRQoL rebounds to general population levels for patients who remain progression-free.

EA6: Alternative weighting of tumour procurement costs

The cost of the surgical resection of tumour tissue was amended to use the proportion of patients having the tumour resection at each site from Study C-144-01[28] as the only weights to estimate the mean cost. The unit costs corresponding to the procedures are still informed by the same codes related to elective

inpatient procedures from NHS Reference Costs 2023/24.[75] When this change is applied, the final cost per day of the procedure increases from [redacted] to [redacted].

EA7: Inclusion of NHS England CAR-T tariff costs

This analysis includes the NHS England 2025/26 CAR-T tariff cost for patients who receive the lifileucel infusion (either within or outside of specifications). This is assumed to cover the costs of tumour tissue procurement, LD chemotherapy administration costs, IL-2 administration and monitoring costs, AEs, 100 days of disease management costs and all other NHS costs relating to the set-up and delivery of lifileucel. The updated costs applied in this analysis are summarised in Table 52.

Table 52: Summary of updated model costs including the NHS England 2025/26 CAR-T tariff

Regimen	Regiment component	% treatment allocation	Company's model		EAG EA7 – including CAR-T tariff	
			Drug/procedure costs per cycle*	Admin costs per cycle*	Drug/procedure costs per cycle*	Admin costs per cycle*
Lifileucel (within specification regimen)	Tumour tissue procurement	100.0%	[redacted]	-	£0.00	-
	LD regimen	100.0%	CP: £144; mesna: £201; FA: £594 (total: £940)	[redacted]	£940	£0.00
	Lifileucel infusion	100.0%	[redacted]	[redacted]	[redacted]	£0.00
	Post-lifileucel infusion (IL-2)	[redacted]	[redacted]	[redacted]	[redacted]	£0.00
	CAR-T tariff	100%	-	-	-	[redacted]
Total cost lifileucel (within specification regimen)			[redacted]	[redacted]	[redacted]	[redacted]
Lifileucel (outside specification regimen)	Tumour tissue procurement	100.0%	[redacted]	-	£0.00	-
	LD regimen	100.0%	CP: £144; mesna: £201; FA: £594 (total: £940)	[redacted]	£940	£0.00
	Lifileucel infusion	0.0%	£0.00	£0.00	£0.00	£0.00
	Post-lifileucel infusion	[redacted]	[redacted]	[redacted]	[redacted]	£0.00
	CAR-T tariff	100%	-	-	-	[redacted]
Total cost lifileucel (outside specification regimen)			[redacted]	[redacted]	[redacted]	[redacted]
Lifileucel (discontinued before infusion)	Tumour tissue procurement	100.0%	[redacted]	-	[redacted]	-
	LD regimen	[redacted]	CP: [redacted]; mesna: [redacted]; FA: [redacted] (total: [redacted])	[redacted]	[redacted]	[redacted]
	CAR-T tariff	-	-	-	-	-
Total cost lifileucel (discontinued before infusion)			[redacted]	[redacted]	[redacted]	[redacted]
Lifileucel (died before infusion)	Tumour tissue procurement	100.0%	[redacted]	[redacted]	[redacted]	[redacted]
	CAR-T tariff	-	-	-	-	-
Total cost lifileucel (died before infusion)			[redacted]	[redacted]	[redacted]	[redacted]

Admin - administration; CP - cyclophosphamide; FA - fludarabine; LD - lymphodepletion; N - number; EAG - External Assessment Group; EA - exploratory analysis; CAR-T - chimeric antigen receptor T-cell

** These values include the application of RDI, wastage, number of admins per treatment cycle, total number of doses/cycles, and treatment allocation*

EA8: EAG-preferred analysis

The EAG's preferred analysis combines EAs 1-7.

Additional sensitivity analyses

The following additional sensitivity analyses were conducted using the deterministic version of the EAG's preferred model (EA8).

- *ASA1a-e:* These analyses apply all alternative fitted MCMs for PFS in the lifileucel group. The generalised gamma MCM is not considered because this model did not converge.
- *ASA2a-f*: These analyses apply all alternative fitted MCMs for OS in the lifileucel group.
- *ASA3:* This analysis applies the inverse unadjusted (naïve) HRs from the company's ITC to lifileucel MCMs for PFS and OS to estimate outcomes for the ipilimumab group ([redacted]). The use of these HRs results in more favourable PFS and OS outcomes for ipilimumab (see Figure 41). This scenario was preferred over the base case analysis by one of the EAG's clinical advisors.
- *ASA4:* This analysis applies an HR for BSC versus chemotherapy of 2.0. This is consistent with the company's base case model.
- *ASA5:* This analysis applies an SMR of 1.57. This is consistent with the company's scenario analysis.
- *ASA6:* This analysis applies a utility value of 0.80 in the PF state and 0.68 in the PD state, based on values reported in TA268, TA321 and TA562.[17, 22, 65] This reflects a larger difference in utility values between the health states compared with the company's base case analysis.
- *ASA7:* This analysis applies a disutility of -0.02 for all long-term survivors who remain progression-free after 5 years. It should be noted that the magnitude of this assumed decrement is arbitrary; this analysis has been conducted to explore the impact of assuming that long-term survivors do not experience a full return to general population HRQoL.
- *ASA8:* This analysis explores the impact of doubling the magnitude of the utility decrement associated with lifileucel administration (disutility = -0.18).
- *ASA9:* This analysis assumes that all non-infused patients receive BSC alone, rather than a mix of ipilimumab, chemotherapy and BSC.
- *ASA10:* This analysis assumes that all patients in the chemotherapy group receive dacarbazine, based on clinical advice received the EAG.
- *ASA11:* This analysis applies non-Reference Case discount rates of 1.5% for health outcomes and costs.
- *ASA12:* This analysis applies a decision modifier of 1.7 for all options including ipilimumab.

5.5.2 Exploratory analyses results

5.5.2.1 Results of the EAG's preferred analysis

The results of the EAG's preferred analysis for the comparison of lifileucel versus ipilimumab are presented in Table 53. Each of analyses EA2-7 include the error corrections included in EA1. All of the EAG's preferred assumptions are combined in EA8. All results reported for this comparison include a decision modifier of 1.2, except the company's base-case. Correcting the remaining errors in the company's updated model leads to an estimated ICER for lifileucel versus ipilimumab of [redacted] per QALY gained (EA1). Changing preferences around the HR for BSC versus chemotherapy, the cure time point and the tumour procurement costs (EA3, EA5 and EA6) have only a minor impact on the ICER. Selecting the log-logistic MCMs for PFS and OS for lifileucel has a more pronounced impact, leading to an increase in the ICER of approximately £2,200 (EA4). Removing the adjustment to the lifileucel MCMs and applying the inverse STC-adjusted HR to the unadjusted lifileucel PFS and OS MCMs to estimate outcomes for ipilimumab group is the key driver of the ICER, leading to an increase of approximately [redacted] per QALY gained (EA2). Another important driver of the ICER is the inclusion of the CAR-T tariff costs for lifileucel, which leads to an increase of approximately £8,400 per QALY gained (EA7). Under the EAG's preferred scenario (EA8), the deterministic ICER for lifileucel versus ipilimumab is estimated to be [redacted] per QALY gained, which is substantially higher than the company's base case ICER.

Table 53: EAG preferred analysis results – lifileucel versus ipilimumab, pairwise comparisons

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER (excl. DM)	ICER (incl. DM)
Company's updated base case model (DM=1.7)								
Lifileucel	8.51	4.07	[redacted]	7.19	3.20	[redacted]	[redacted]	[redacted]
Ipilumumab	1.32	0.87	[redacted]	-	-	-	-	-
EA1: Correction of errors (DM=1.2)								
Lifileucel	8.55	4.08	[redacted]	7.23	3.21	[redacted]	[redacted]	[redacted]
Ipilumumab	1.32	0.87	[redacted]	-	-	-	-	-
EA2: Application of inverse STC-adjusted HR to unadjusted lifileucel PFS and OS MCMs to estimate outcomes for ipilimumab group (DM=1.2)								
Lifileucel	5.84	2.89	[redacted]	4.06	1.91	[redacted]	[redacted]	[redacted]
Ipilumumab	1.77	0.98	[redacted]	-	-	-	-	-
EA3: Application of HR for BSC versus chemotherapy of 1.0 (DM=1.2)								
Lifileucel	8.63	4.14	[redacted]	7.31	3.27	[redacted]	[redacted]	[redacted]
Ipilumumab	1.32	0.87	[redacted]	-	-	-	-	-
EA4: Use of log-logistic MCMs for lifileucel PFS and OS (DM=1.2)								
Lifileucel	7.64	3.80	[redacted]	6.32	2.93	[redacted]	[redacted]	[redacted]
Ipilumumab	1.32	0.87	[redacted]	-	-	-	-	-
EA5: Cure time point = 5 years (DM=1.2)								
Lifileucel	8.55	4.06	[redacted]	7.23	3.18	[redacted]	[redacted]	[redacted]
Ipilumumab	1.32	0.87	[redacted]	-	-	-	-	-
EA6: Alternative weighting of tumour procurement costs (DM=1.2)								
Lifileucel	8.55	4.08	[redacted]	7.23	3.21	[redacted]	[redacted]	[redacted]
Ipilumumab	1.32	0.87	[redacted]	-	-	-	-	-
EA7: Inclusion of NHS tariff costs for lifileucel (DM=1.2)								
Lifileucel	8.55	4.08	[redacted]	7.23	3.21	[redacted]	[redacted]	[redacted]
Ipilumumab	1.32	0.87	[redacted]	-	-	-	-	-
EA8: EAG-preferred analysis (EAs 1-7 combined) (DM=1.2)								
Lifileucel	5.15	2.67	[redacted]	3.65	1.79	[redacted]	[redacted]	[redacted]
Ipilumumab	1.50	0.88	[redacted]	-	-	-	-	-

** Undiscounted*
LYG – life year gained; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio; DM – decision modifier; Inc. – incremental; NR – not reported

The results of the EAG's preferred analysis for the comparison of lifileucel versus chemotherapy and versus BSC are presented in Table 54. All results reported for these comparisons are based on pairwise analyses and all analyses include a decision modifier of 1.7. The results indicate that correcting the remaining errors in the company's updated model leads to ICERs for lifileucel versus chemotherapy and lifileucel versus BSC of [redacted] per QALY gained and [redacted] per QALY gained, respectively (EA1). None of the individual EAs have a substantial impact on the ICER (<£1,000), except for the application of HR for BSC versus chemotherapy of 1.0, which results in a similar ICER for lifileucel against both comparators of approximately [redacted] per QALY gained (EA3), the use of log-logistic MCMs for lifileucel PFS and OS, which increases in the ICERs against chemotherapy and BSC by approximately £5,500 and £4,500, respectively (EA4), and the inclusion of the CAR-T tariff costs for lifileucel, which increases in the ICERs against chemotherapy and BSC by approximately

£8,000 and £7,200, respectively (EA7). Under the EAG's preferred assumptions (EA8), the deterministic ICER for lifileucel versus chemotherapy is estimated to be [redacted] per QALY gained, and the ICER for lifileucel versus BSC is estimated to be [redacted] per QALY gained.

Table 54: EAG preferred analysis results – lifileucel versus chemotherapy and lifileucel versus BSC, pairwise comparisons, decision modifier 1.7

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER (excl. DM)	ICER (incl. DM)
Company's updated base case model								
Lifileucel	5.78	2.87	[redacted]	-	-	-	-	-
Chemotherapy	0.79	0.56	[redacted]	4.98	2.31	[redacted]	[redacted]	[redacted]
BSC	0.41	0.29	[redacted]	5.37	2.58	[redacted]	[redacted]	[redacted]
EA1: Correction of errors								
Lifileucel	5.81	2.88	[redacted]	-	-	-	-	-
Chemotherapy	0.79	0.56	[redacted]	5.01	2.32	[redacted]	[redacted]	[redacted]
BSC	0.41	0.29	[redacted]	5.40	2.59	[redacted]	[redacted]	[redacted]
EA2: Application of inverse STC-adjusted HR to unadjusted lifileucel PFS and OS MCMs to estimate outcomes for ipilimumab group								
Lifileucel	5.84	2.89	[redacted]	-	-	-	-	-
Chemotherapy	0.79	0.56	[redacted]	5.04	2.32	[redacted]	[redacted]	[redacted]
BSC	0.41	0.29	[redacted]	5.43	2.59	[redacted]	[redacted]	[redacted]
EA3: Application of HR for BSC versus chemotherapy of 1.0								
Lifileucel	5.88	2.93	[redacted]	-	-	-	-	-
Chemotherapy	0.79	0.56	[redacted]	5.09	2.37	[redacted]	[redacted]	[redacted]
BSC	0.79	0.56	[redacted]	5.09	2.37	[redacted]	[redacted]	[redacted]
EA4: Use of log-logistic MCMs for lifileucel PFS and OS								
Lifileucel	5.06	2.64	[redacted]	-	-	-	-	-
Chemotherapy	0.79	0.56	[redacted]	4.26	2.07	[redacted]	[redacted]	[redacted]
BSC	0.41	0.29	[redacted]	4.65	2.34	[redacted]	[redacted]	[redacted]
EA5: Cure time point = 5 years								
Lifileucel	5.81	2.86	[redacted]	-	-	-	-	-
Chemotherapy	0.79	0.56	[redacted]	5.01	2.30	[redacted]	[redacted]	[redacted]
BSC	0.41	0.29	[redacted]	5.40	2.57	[redacted]	[redacted]	[redacted]
EA6: Alternative weighting of tumour procurement costs								
Lifileucel	5.81	2.88	[redacted]	-	-	-	-	-
Chemotherapy	0.79	0.56	[redacted]	5.01	2.32	[redacted]	[redacted]	[redacted]
BSC	0.41	0.29	[redacted]	5.40	2.59	[redacted]	[redacted]	[redacted]
EA7: Inclusion of NHS tariff costs for lifileucel								
Lifileucel	5.81	2.88	[redacted]	-	-	-	-	-
Chemotherapy	0.79	0.56	[redacted]	5.01	2.32	[redacted]	[redacted]	[redacted]
BSC	0.41	0.29	[redacted]	5.40	2.59	[redacted]	[redacted]	[redacted]
EA8: EAG-preferred analysis (EA1-7 combined)								
Lifileucel	5.15	2.67	[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]

LYG – life year gained; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio; DM – decision modifier; Inc. – incremental; NR – not reported
** Undiscounted*

5.5.2.2 Results of the EAG's additional sensitivity analysis

The results of the EAG's additional sensitivity analyses for the pairwise comparisons of lifileucel versus ipilimumab, chemotherapy and BSC are presented in Table 55, Table 56, and Table 57, respectively. Most scenarios have only a modest impact on the ICER. The exceptions are the application of non-Reference Case discount rates of 1.5% and a decision modifier of 1.7 (for ipilimumab only). These analyses result in lower ICERs for lifileucel versus ipilimumab of [redacted] and [redacted] per QALY gained, respectively. The use of discount rates of 1.5% results in ICERs for lifileucel versus chemotherapy of [redacted] per QALY gained, and lifileucel versus BSC of [redacted] per QALY gained.

Table 55: EAG's additional sensitivity analysis results, lifileucel versus ipilimumab, pairwise comparison, deterministic

Scenario	Description	Lifileucel versus ipilimumab				
		Inc. QALYs	Inc. Costs	ICER excl. DM	ICER incl. DM	DM
EA8	**EAG preferred deterministic model**	1.79	[redacted]	[redacted]	[redacted]	1.2
ASA1a	Lifiluecel PFS – exponential MCM	1.81	[redacted]	[redacted]	[redacted]	1.2
ASA1b	Lifiluecel PFS – Weibull MCM	1.82	[redacted]	[redacted]	[redacted]	1.2
ASA1c	Lifiluecel PFS – Gompertz MCM	1.81	[redacted]	[redacted]	[redacted]	1.2
ASA1d	Lifiluecel PFS – log-logistic MCM	1.79	[redacted]	[redacted]	[redacted]	1.2
ASA1e	Lifiluecel PFS – log-normal MCM	1.80	[redacted]	[redacted]	[redacted]	1.2
ASA2a	Lifiluecel OS – exponential MCM	1.94	[redacted]	[redacted]	[redacted]	1.2
ASA2b	Lifiluecel OS – Weibull MCM	1.95	[redacted]	[redacted]	[redacted]	1.2
ASA2c	Lifiluecel OS – Gompertz MCM	1.94	[redacted]	[redacted]	[redacted]	1.2
ASA2d	Lifiluecel OS – log-logistic MCM	1.79	[redacted]	[redacted]	[redacted]	1.2
ASA2e	Lifiluecel OS – log-normal MCM	1.72	[redacted]	[redacted]	[redacted]	1.2
ASA2f	Lifiluecel OS – generalised gamma MCM	1.88	[redacted]	[redacted]	[redacted]	1.2
ASA3	Inverse unadjusted HRs from company's ITC applied to lifileucel MCMs	1.12	[redacted]	[redacted]	[redacted]	1.2
ASA4	BSC vs chemtherapy HR=2.0	1.74	[redacted]	[redacted]	[redacted]	1.2
ASA5	SMR=1.57	1.70	[redacted]	[redacted]	[redacted]	1.2
ASA6	Progression-free utility value = 0.80 and post-progression utility = 0.68	1.81	[redacted]	[redacted]	[redacted]	1.2
ASA7	Long-term survivor utility decrement = 0.02	1.77	[redacted]	[redacted]	[redacted]	1.2
ASA8	Lifileucel administration disutility doubled	1.79	[redacted]	[redacted]	[redacted]	1.2
ASA9	Non-infused patients receive BSC	1.77	[redacted]	[redacted]	[redacted]	1.2
ASA10	All chemotherapy patients receive dacarbazine	1.79	[redacted]	[redacted]	[redacted]	1.2
ASA11	Discount rates = 1.5%	2.27	[redacted]	[redacted]	[redacted]	1.2
ASA12	Decision modifier = 1.7	1.79	[redacted]	[redacted]	[redacted]	1.7

ASA - additional sensitivity analysis; BSC - best supportive care; DM - decision modifier; EAG - External Assessment Group; EA - exploratory analysis; HR - hazard ratio; ICER - incremental cost-effectiveness ratio; ITC - indirect treatment comparison; MCM - mixture-cure model; N/a – not applicable; QALY - quality-adjusted life year.

Table 56: EAG's additional sensitivity analysis results, lifileucel versus chemotherapy, pairwise comparison, deterministic

Scenario	Description	Lifileucel versus chemotherapy				
		Inc. QALYs	Inc. Costs	ICER excl. DM	ICER incl. DM	DM
EA8	**EAG preferred deterministic model**	2.11	[redacted]	[redacted]	[redacted]	1.7
ASA1a	Lifiluecel PFS – exponential MCM	2.13				1.7
ASA1b	Lifiluecel PFS – Weibull MCM	2.14				1.7
ASA1c	Lifiluecel PFS – Gompertz MCM	2.13				1.7
ASA1d	Lifiluecel PFS – log-logistic MCM	2.11				1.7
ASA1e	Lifiluecel PFS – log-normal MCM	2.11				1.7
ASA2a	Lifiluecel OS – exponential MCM	2.36				1.7
ASA2b	Lifiluecel OS – Weibull MCM	2.38				1.7
ASA2c	Lifiluecel OS – Gompertz MCM	2.36				1.7
ASA2d	Lifiluecel OS – log-logistic MCM	2.11				1.7
ASA2e	Lifiluecel OS – log-normal MCM	2.00				1.7
ASA2f	Lifiluecel OS – generalised gamma MCM	2.25				1.7
ASA3	Inverse unadjusted HRs from company's ITC applied to lifileucel MCMs	2.16				1.7
ASA4	BSC vs chemotherapy HR=2.0	2.06				1.7
ASA5	SMR=1.57	2.01				1.7
ASA6	Progression-free utility value = 0.80 and post-progression utility = 0.68	2.13				1.7
ASA7	Long-term survivor utility decrement = 0.02	2.08				1.7
ASA8	Lifileucel administration disutility doubled	2.11				1.7
ASA9	Non-infused patients receive BSC	2.09				1.7
ASA10	All chemotherapy patients receive dacarbazine	2.11				1.7
ASA11	Discount rates = 1.5%	2.66				1.7
ASA12	Decision modifier = 1.7	N/a	N/a	N/a	N/a	N/a

ASA - additional sensitivity analysis; BSC - best supportive care; DM - decision modifier; EAG - External Assessment Group; EA - exploratory analysis; HR - hazard ratio; ICER - incremental cost-effectiveness ratio; ITC - indirect treatment comparison; MCM - mixture-cure model; N/a – not applicable; QALY - quality-adjusted life year.

Table 57: EAG's additional sensitivity analysis results, lifileucel versus BSC, pairwise comparison, deterministic

Scenario	Description	Lifileucel versus BSC				
		Inc. QALYs	Inc. Costs	ICER excl. DM	ICER incl. DM	DM
EA8	**EAG preferred deterministic model**	2.11	[redacted]	[redacted]	[redacted]	1.7
ASA1a	Lifiluecel PFS – exponential MCM	2.13				1.7
ASA1b	Lifiluecel PFS – Weibull MCM	2.14				1.7
ASA1c	Lifiluecel PFS – Gompertz MCM	2.13				1.7
ASA1d	Lifiluecel PFS – log-logistic MCM	2.11				1.7
ASA1e	Lifiluecel PFS – log-normal MCM	2.11				1.7
ASA2a	Lifiluecel OS – exponential MCM	2.36				1.7
ASA2b	Lifiluecel OS – Weibull MCM	2.38				1.7
ASA2c	Lifiluecel OS – Gompertz MCM	2.36				1.7
ASA2d	Lifiluecel OS – log-logistic MCM	2.11				1.7
ASA2e	Lifiluecel OS – log-normal MCM	2.00				1.7
ASA2f	Lifiluecel OS – generalised gamma MCM	2.25				1.7
ASA3	Inverse unadjusted HRs from company's ITC applied to lifileucel MCMs	2.16				1.7
ASA4	BSC vs chemtherapy HR=2.0	2.33				1.7
ASA5	SMR=1.57	2.01				1.7
ASA6	Progression-free utility value = 0.80 and post-progression utility = 0.68	2.13				1.7
ASA7	Long-term survivor utility decrement = 0.02	2.08				1.7
ASA8	Lifileucel administration disutility doubled	2.11				1.7
ASA9	Non-infused patients receive BSC	2.09				1.7
ASA10	All chemotherapy patients receive dacarbazine	2.11				1.7
ASA11	Discount rates = 1.5%	2.66				1.7
ASA12	Decision modifier = 1.7	N/a	N/a	N/a	N/a	N/a

ASA - additional sensitivity analysis; BSC - best supportive care; DM - decision modifier; EAG - External Assessment Group; EA - exploratory analysis; HR - hazard ratio; ICER - incremental cost-effectiveness ratio; ITC - indirect treatment comparison; MCM - mixture-cure model; N/a – not applicable; QALY - quality-adjusted life year.

5.6 Discussion

The CS[1] presents an SLR of existing economic studies of treatments for adult patients with previously treated, unresectable or metastatic melanoma. None of the identified studies include lifileucel as the intervention. The previous NICE TAs included in the company's review highlight a range of alternative approaches for extrapolating survival outcomes, including assumptions of cure for patients receiving certain therapies (particularly those receiving ipilimumab, nivolumab or pembrolizumab).

The company's submitted model assesses the cost-effectiveness of lifileucel versus ipilimumab, chemotherapy and BSC for [redacted]. For patients who receive the lifileucel infusion or the comparator therapies, the economic analysis uses a partitioned survival approach which includes three health states: (i) PF; (ii) PD and (iii) dead. The model includes an initial decision tree component which accounts for patients who do not receive a within-specification lifileucel infusion; patients who do not receive the infusion or who receive an out-of-specification infusion are assumed to accrue a weighted average of the outcomes for the comparators. The economic analysis adopts an NHS and PSS perspective, including QALYs accrued by melanoma patients; caregiver effects are not included. Clinical outcomes for the lifileucel-infused patients are based on MCMs fitted to data on PFS and OS from the PDAwCS population of Study C-144-01,[28] whereas outcomes for the ipilimumab and chemotherapy groups are informed by published cohort studies.[30, 52] Outcomes for BSC were modelled by applying an HR of 2.0 to the parametric survival models for the chemotherapy group. The lifileucel MCMs are adjusted using HRs obtained from the company's ITC in the comparison against ipilimumab; the comparisons against chemotherapy and BSC are (naïve) unadjusted comparisons. Health state utility values are based on an unweighted average of utility values for PF and PD states in published models and previous NICE TAs of treatments for advanced melanoma. Resource costs are informed by a range of sources including standard costing sources, published literature, clinical input and assumptions. Model results are presented in the CS[1] in the form of pairwise comparisons between lifileucel and each comparator; a fully incremental anlaysis is not presented.

The probabilistic version of the company's original model suggests the following results:

- *Lifileucel versus ipilimumab (STC-adjusted).* Compared against ipilumumab, lifileucel is expected to generate an additional 3.73 QALYs at an additional cost of [redacted]. Based on a decision modifier of 1.7, the ICER for lifileucel is expected to be [redacted] per QALY gained.

- *Lifileucel versus chemotherapy (naïve ITC):* Compared against chemotherapy, lifileucel is expected to generate an additional 2.69 QALYs at an additional cost of [redacted]. Based on a decision modifier of 1.7, the ICER for lifileucel is expected to be [redacted] per QALY gained.
- *Lifileucel versus BSC (naïve ITC):* Compared against BSC, lifileucel is expected to generate an additional 2.97 QALYs at an additional cost of [redacted]. Based on a decision modifier of 1.7, the ICER for lifileucel is expected to be [redacted] per QALY gained.

For all three pairwise comparisons, the deterministic ICERs are around £3,000 to £6,000 higher than the probabilistic ICERs.

The probabilistic version of the company's revised model provided as part of the clarification response suggests pairwise ICERs for lifileucel versus ipilimumab, chemotherapy and BSC of [redacted], [redacted] and [redacted] per QALY gained, respectively. The corresponding ICERs based on the deterministic version of the revised model are higher at [redacted], [redacted] and [redacted] per QALY gained.

The EAG critically appraised the company's health economic analysis and double-programmed the deterministic version of the company's original model. The EAG's main concerns regarding the company's economic model are summarised below:

- The EAG has concerns about the company's adjusted comparison of lifileucel versus ipilimumab. The company's modelling approach results in implied cure fractions for lifileucel (in the da Silva ipilimumab population) which are substantially higher that those estimated from fitting MCMs directly to data from Study C-144-01 (adjusted cure fractions: PFS – [redacted], OS – [redacted]). These cure fractions substantially exceed clinical expectations of cure (estimated to be [redacted] by clinical experts consulted by the company). In addition, clinical experts have suggested that some patients receiving ipilimumab may achieve long-term survival. However, follow-up in the external study used to inform ipilimumab PFS and OS (da Silva *et al.*) was short and the company only fitted standard parametric survivals to the data. These models do not reflect the possibility of cure for ipilimumab-treated patients and therefore do not align with clinical expectations.
- The company's model assumes that chemotherapy is more effective than BSC (HR = 2.0). However, an unspecified number of clinicians attending the advisory board meeting suggested that chemotherapy confers no additional treatment effect. The EAG's clinical advisors agreed with this view.
- The CS[1] does not report on outcomes for patients in Study C-144-01[28] who did not receive the lifileucel infusion. The company's model applies a weighted average of health outcomes and

costs associated with the comparator therapies to non-infused patients. In the absence of further data, it is unclear whether this assumption leads to credible predictions of OS for patients who do not receive the infusion.

- The EAG disagrees with the company's selection of the log-normal MCM for PFS and the exponential MCM for OS. The EAG prefers the log-logistic MCMs for both endpoints.
- The EAG considers the company's decision to apply unweighted mean utility values from published studies and NICE TAs to be unconventional and subject to uncertainty.
- The results of the economic analysis presented in the CS[28] apply a decision modifier of 1.7 for all comparisons. However, based on the York Shortfall Calculator, a decision modifier of 1.2 should be applied in the comparison against ipilimumab.
- The company's model applies administration costs based on NHS Reference Costs and excludes additional costs relating to the set-up, implementation, logistics and delivery of lifileucel. Following advice from NHS England, the EAG's preferred analysis includes the NHS England 2025/26 CAR-T tariff cost of [redacted] for patients who receive the lifileucel infusion.

The EAG also identified further issues relating to model programming errors and several other cost and utility parameters values. In addition, the EAG considers the results of the company's PSA to be unreliable.

The EAG undertook exploratory analyses using the company's revised model to address some of the issues described above. The EAG's preferred model includes: (i) the correction of errors; (ii) the removal of the company's adjustment of the lifileucel MCMs and the application of the inverse STC-adjusted HR to the lifileucel MCMs to estimate outcomes for ipilimumab; (iii) the application of an HR of 1.0 for BSC versus chemotherapy; (iv) the use of log-logistic MCMs for lifleucel PFS and OS; (v) an assumed cure time point of 5 years; (vi) the inclusion of an alternative weighting of tumour procurement costs and (vii) the inclusion of the NHS CAR-T tariff. The deterministic version of the EAG's preferred model suggests the following results.

- *Lifleucel versus ipilimumab.* Based on a decision modifier of 1.2, the ICER for lifileucel versus ipilimumab is estimated to be [redacted] per QALY gained.
- *Lifleucel versus chemotherapy.* Based on a decision modifier of 1.7, the ICER for lifileucel versus chemotherapy is estimated to be [redacted] per QALY gained.
- *Lifleucel versus BSC.* Based on a decision modifier of 1.7, the ICER for lifileucel versus BSC is estimated to be [redacted] per QALY gained.

The EAG's preferred ICERs for all three comparisons are higher than the ICERs estimated by the company.

The EAG's additional sensitivity analyses indicate that the ICER for lifleucel is particularly sensitive to the discount rates and the decision modifier.

6. CONCLUSIONS

Clinical effectiveness conclusions

The CS presents data from one pivotal, single-arm study (C-144-01) evaluating lifileucel in adults (≥18 years) with stage IIIC or IV melanoma who had progressed after at least one prior systemic therapy, including a PD-1 inhibitor and, if BRAF V600 mutation-positive, a BRAF inhibitor (with or without a MEK inhibitor). The CS focuses only on patients who received cryopreserved lifileucel (generation 2) meeting manufacturing product specifications (Cohorts 2 and 4). The PDAwCS efficacy set included [redacted] who received lifileucel within the proposed SmPC dosing range and manufactured at facilities approved for commercial supply. As of the 30th June 2023 DCO (median follow-up = [redacted]), pooled results from Cohorts 2 and 4 (PDAwCS efficacy set) demonstrated an ORR of [redacted], as assessed by an IRC. CR was achieved in [redacted], PR in [redacted] and SD was observed in [redacted] patients. Median IRC-assessed PFS was [redacted] and median OS was [redacted]. The most common Grade 3/4 AEs included: [redacted]

Due to the absence of head-to-head randomised studies, the company undertook an STC comparing lifileucel versus ipilimumab and an unadjusted (naïve) ITC comparing lifileucel versus chemotherapy. The adjusted HRs for lifileucel versus ipilimumab from the STC were estimated to be [redacted] The unadjusted HRs for lifileucel versus chemotherapy were estimated to be [redacted].

Cost-effectiveness conclusions

The company's model assesses the cost-effectiveness of lifileucel versus ipilimumab, chemotherapy and BSC for the treatment of [redacted] All comparisons are pairwise in nature; a fully incremental analysis was not presented. The deterministic version of the company's revised model provided as part of the clarification response suggests pairwise ICERs for

lifileucel versus ipilimumab, chemotherapy and BSC of [redacted], [redacted] and [redacted] per QALY gained, respectively (including a decision modifier of 1.7 for all comparisons).

The EAG's preferred model includes: (i) the correction of errors; (ii) the removal of the company's adjustment of the lifileucel MCMs and the application of the inverse STC-adjusted HR to the lifileucel MCMs to estimate outcomes for ipilimumab; (iii) the application of an HR of 1.0 for BSC versus chemotherapy; (iv) the use of log-logistic MCMs for lifleucel PFS and OS; (v) an assumed cure time point of 5 years; (vi) the inclusion of an alternative weighting of tumour procurement costs and (vii) the inclusion of the NHS CAR-T tariff. The EAG's preferred analysis suggests pairwise ICERs for lifileucel versus ipilimumab, chemotherapy and BSC of [redacted], [redacted] and [redacted] per QALY gained, respectively (including a decision modifier of 1.2 for the comparison against ipilimumab and a decision modifier of 1.7 for the comparisons against chemotherapy and BSC).

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Lifileucel for previously treated unresectable or metastatic melanoma [ID3863]

External Assessment Group report addendum: Additional analysis of data from Study C144-01 patients who did not receive the lifileucel infusion

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1. Introduction

The company's economic model assumes that amongst the population of patients in whom the lifileucel infusion is planned, [redacted] will not receive the within-specification infusion. These patients are assumed to receive one of the model comparators, with costs and outcomes based on a weighted mean of those for the model comparator groups (weighting: ipilimumab [redacted], chemotherapy [redacted] or BSC [redacted]). The company's submission (CS)[1] did not contain any information on the observed survival outcomes for patients in Study C-144-01[2] who did not receive the within-specification lifileucel infusion. As such, the EAG considered the appropriateness of the assumptions applied in the company's model to be unclear. During the clarification process, the EAG asked the company to provide Kaplan-Meier plots of progression-free survival (PFS) and overall survival (OS) for people in Cohorts 2 and 4 of Study C-144-01 who did not receive the infusion. The company was unable to provide these plots within the timescales for submission of the final EAG report. Owing to the lack of evidence to support the company's modelling assumptions, this was raised as a key issue in the final EAG report. In August 2025, the company submitted Kaplan-Meier plots of PFS and OS for patients who underwent tumour harvesting but who did not receive the infusion; these data are shown in Figure 1 and Figure 2, respectively. The data include [redacted] patients who did not receive the lifileucel infusion for both end points; Figure 7 of the CS indicates that [redacted] patients were not infused. The EAG was initially unsure why [redacted] patients are not represented in the PFS and OS datasets. The company subsequently provided additional information at the FAC stage stating that: *"Treatment rechallenging with anti-PD-1 therapies or BRAF+/-MEK inhibitors is not reimbursed in UK, and these two classes of treatments were not considered to be relevant comparators for this evaluation. Therefore, the derived data excluded [redacted] patients (out of [redacted]) who received Pembrolizumab, Nivolumab, Nivolumab + Ipilimumab, or BRAF+/-MEK inhibitors after not being infused with lifileucel despite being tumor-harvested."*

Figure 1: Kaplan-Meier plot of progression-free survival in the subgroup of patients within the PDAwCS with the following characteristics: Tumour harvested, not infused with lifileucel and not received anti-PD-1 (nivolumab, pembrolizumab or nivolumab plus ipilimumab) or BRAF+/-MEK inhibitors after tumour harvesting

PDAwCS - Pooled Data Aligned with Commercial Specifications; PD-1 - programmed death 1; MEK - mitogen-activated protein kinase kinase

Figure 2: Kaplan-Meier plot of overall survival in the subgroup of patients within the PDAwCS with the following characteristics: Tumour harvested, not infused with lifileucel and not received anti-PD-1 (nivolumab, pembrolizumab or nivolumab plus ipilimumab) or BRAF+/-MEK inhibitors after tumour harvesting

PDAwCS - Pooled Data Aligned with Commercial Specifications; PD-1 - programmed death 1; MEK - mitogen-activated protein kinase kinase

2. Additional analysis undertaken by the EAG

2.1 Estimation of restricted mean survival time for PFS and OS

The EAG digitised the available PFS and OS data and estimated the restricted mean survival time (RMST) using the *Survival* package in R. The EAG then compared the estimated RMST for PFS and OS using the digitised data against the mean PFS and OS predictions obtained from the EAG's preferred analysis of the company's economic model (see EAG report,[3] Table 54, Exploratory Analysis 8). The estimates of PFS and OS are shown in Table 1. Estimated RMST for PFS in non-infused patients in Study C144-01 is [redacted]; this is lower than the estimate of 0.41 years spent alive in the progression-free state in the company's economic model. Estimated RMST for OS in non-infused patients in Study C144-01 is [redacted]; this is lower than the estimate of 0.97 years spent in either of the alive states in the company's economic model. The EAG notes that the standard errors around the RMST estimates are fairly large. In addition, the RMST will likely underestimate of the overall mean OS time because some patients remained alive at the end of follow-up. Overall, the EAG believes that the additional data on patients who did not receive the within-specification lifileucel infusion in Study C144-01 provide broad support for the assumptions employed in the company's model.

Table 1: Comparison of mean PFS and OS – non-infused patients in Study C144-01 and EAG-preferred analysis of the company's model

Outcome	Probability	PFS (years)	OS (years)
Model - BSC	[redacted]	0.41	0.79
Model - chemotherapy	[redacted]	0.41	0.79
Model - ipilimumab	[redacted]	0.41	1.50
Model - weighted estimate of BSC, chemotherapy and ipilimumab	-	**0.41**	**0.97**
Study C-144-01 – RMST	-	[redacted]	[redacted]

BSC - best supportive care; PFS - progression-free survival; OS - overall survival; RMST - restricted mean survival time

2.2 Impact of shrinking modelled PFS and OS for patients who do not receive the within-specification infusion on the ICERs for lifileucel

In order to address any remaining uncertainty, the EAG amended the company's economic model to shrink the estimates of mean PFS and OS for patients who do not receive the within-specification lifileucel infusion to match the RSMT estimates from Study C-144-01[2] (see Table 1). This was done by applying manually-derived hazard ratios (HRs) to the per-cycle PFS and OS estimates for the group of patients who did not receive lifileucel and instead received the comparators (ipilimumab, chemotherapy and BSC). The same HRs were applied separately to the estimates for each comparator in those patients who did not receive the within-specification infusion (PFS HR = 1.4; OS HR = 1.14). The results of this analysis are shown in Table 2. As shown in the table, including lower PFS and OS estimates for patients who do not receive the infusion increases the ICERs for lifileucel versus ipilimumab,

chemotherapy and BSC, although the effect is small for each comparison. Consequently, the EAG no longer considers this to reflect a key issue for decision-making.

Table 2: EAG preferred and additional analyses results – lifileucel versus ipilimumab, chemotherapy and BSC, pairwise comparisons

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER (excl. DM)	ICER (incl. DM)
EA8: EAG-preferred analysis (EAs 1-7 combined) (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]
Additional analysis: EAG-preferred analysis (EA8) + PFS and OS for lifileucel non-infused patients in Study C144-01 (DM=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]

** Undiscounted*

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; DM - decision modifier; Inc. - incremental; NR - not reported

3. References

1. Iovance Biotherapeutics. Lifileucel for previously treated unresectable or metastatic melanoma [ID3863]. Company evidence submission. Iovance: Altrincham, UK; 2025.
2. Iovance Biotherapeutics. Study C-144-01 clinical pack (containing CSR, addendum CSR and PDAwCS efficacy). A Phase 2, prospective, multicentre, open-label, single-arm clinical study evaluating the use of lifileucel in patients with advanced (unresectable or metastatic) melanoma who progressed on or after anti–PD-1/PD-L1 therapy. Iovance: Altrincham, UK; 2023.
3. Navega Biz A, Pandor A, Daly G, Tappenden P, Ren S, Pulsford E*, et al.* Lifileucel for previously treated unresectable or metastatic melanoma [ID3863]. External Assessment Group report. University of Sheffield: Sheffield, UK; 2025.

Single Technology Appraisal

Lifileucel for previously treated unresectable or metastatic melanoma ID3863

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as [redacted] in pink.

Issue 1 BRAF correction

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
BRAF is not an acronym Pages 10,13	• Remove BRAF in abbreviation list • Do not refer to BRAF by another name	BRAF is not an acronym, it is the name of a gene.	The EAG report has been amended as suggested, and in other instances of the report (pages 27, 35, 46, 97 and 98).

Issue 2 MEK correction

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
MEK incorrectly expanded Pages 11,13	• MEK should be referred to as Mitogen-activated protein kinase kinase • MEK is not expanded in our proposed SMPC indication, and should not be expanded in this document	For accuracy and to align with proposed SMPC indication.	The EAG report has been amended as suggested. MEK is now expanded correctly elsewhere in the report including in table footnotes (but not in the wording of the anticipated license).

Issue 3 Ipilimumab cure consideration in company model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report incorrectly states that the company's model does not consider a possibility of a cure for ipilimumab-treated patients Page 19	Remove or correct: "As such, the company's model does not reflect the possibility of cure in ipilimumab-treated patients"	There is functional cure assumption in the model. Ipi-treated Patients who are progression free by year 3 start following general population mortality trend. The Company did not apply a mixture cure model to this population but the CE analysis still considers the possibility of cure for Ipi-treated patients.	The EAG agrees that the text should be amended to improve clarity. The highlighted sentence has been removed and replaced with the following text: *"The model assumes that [redacted] of ipilimumab-treated patients are cured for OS, but no patients are cured for PFS. Including this cure assumption has a negligible impact on mean OS in the ipilimumab group (mean OS including cure assumption = 1.322 years; mean OS excluding cure assumption = 1.321 years). As such, the EAG considers that the company's model does*

			not fully reflect the possibility of cure for ipilimumab-treated patients."

Issue 4 ICER numbers redaction

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
ICER numbers should be redacted Multiple pages throughout document	Redact all ICERs numbers reported	ICERs can be marked confidential to allow other numerical data which is fundamental to decision making to be unmarked. LYGs and QALYs are unredacted so ICERs can be redacted.	The redaction has been updated as suggested.

Issue 5 ICER charts redaction

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Charts containing ICERs should be redacted Pages 151, 152	Redact Figures 32,33,34	ICERs can be marked confidential to allow other numerical data which is fundamental to decision making to be unmarked. LYGs and QALYs are	LYGs and QALYs are now unredacted throughout the report. Figures 32, 33 and 34 (containing the DSA results for lifileucel

		unredacted so ICERs can be redacted.	versus ipilimumab, chemotherapy and BSC, respectively) were already marked as confidential in the EAG report. No additional amendments were necessary.

Issue 6 QALY/LYG unredaction

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
QALYs and LYGs should be unredacted Multiple pages throughout document	Unredact all QALYs and LYGs	LYGs and QALYs are unredacted to allow public numerical data that is fundamental to decision making.	The redaction has been updated as suggested.

Issue 7 Incremental cost numbers redaction

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Incremental Costs numbers should be redacted	Redact all incremental cost numbers	All incremental costs should be redacted as these are a component of ICERs.	Incremental costs were already marked as confidential throughout the EAG report. No

Multiple pages throughout document			additional amendments were necessary.

Issue 8 Probably of net benefit redaction

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Information showing probability of lifileucel generating more net benefit than ipilimumab should be redacted Page 148, 149, 150	• Redact figures (zero and 0.64) • Redact charts (Figure 29, 30,31)	This probability is a function of the ICER which should be redacted.	The redaction has been updated as suggested.

Issue 9 CAR-T tariff redaction

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
CAR-T tariff may need to be redacted if not public Page 177, 188	Redact CAR-T tariff numbers	Consider redacting this number if it is non-public.	The redaction has been updated as suggested.

Issue 10 Long-term lifileucel survival projections redaction

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Observed trend and long-term projections for PFS and OS for lifileucel-treated patients in PDAwCS are not public information Page 123,124	Redact Figures 27 and 28	Raw survival data for patients in PDAwCS have been shared with authorities but not published yet by the company. As Figures 27 and 28 provides information on the observed survival trend in the trial, and involves subjectivity around the long-term survival trend of the patients in PDAwCS (due to choice of model) redaction will protect the confidentiality of the data.	The redaction has been updated as suggested.

Issue 11 MHRA approval correction

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
MHRA approval no longer [redacted] due to delay Page 16	Change MHRA approval date to [redacted]	Updated timelines.	The timelines for MHRA approval have been updated, as advised by the company.

Single Technology Appraisal

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If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 3 October** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as [redacted] in pink.

Issue 1 Clarification on [redacted] patients not included in analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The report stated: "The EAG is unsure why [redacted] patients are not represented in the PFS and OS datasets."	Removal or update based on Iovance information shared.	Within the email from Iovance to NICE on [redacted]: "Treatment rechallenging with anti-PD-1 therapies or BRAF+/-MEK inhibitors is not reimbursed in UK, and these two classes of treatments were not considered to be relevant comparators for this evaluation. Therefore, the derived data excluded [redacted] patients (out of [redacted]) who received Pembrolizumab, Nivolumab, Nivolumab + Ipilimumab, or BRAF+/-MEK inhibitors after not being infused with lifileucel despite being tumor-harvested."	Thank you for the clarification. This information has not been sent to the EAG. The addendum has been amended accordingly to include the additional information.

Issue 2 Redaction: [redacted] patients not included in analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Mark [redacted] as confidential, within the statement: "The EAG is unsure why [redacted]	"The EAG is unsure why [redacted] patients are not represented in the PFS and OS datasets."	Non-public information	This is not a factual inaccuracy issue. The information was already

patients are not represented in the PFS and OS datasets.”			marked as CIC in the EAG’s addendum.