NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Lifileucel for previously treated unresectable or metastatic melanoma

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using lifileucel in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: December 2025

Note that this document is not NICE's final guidance on lifileucel. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using lifileucel in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 22 January 2026
- Second evaluation committee meeting: To be determined
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Lifileucel should not be used for previously treated unresectable or metastatic melanoma (Stage IIIc to Stage IV) in adults who have had:

- a PD-1 blocking antibody, and
- a BRAF inhibitor with or without a MEK inhibitor, if the cancer is BRAF V600 mutation positive.

1.2 This recommendation is not intended to affect treatment with lifileucel that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

What this means in practice

Lifileucel is not required to be funded and should not be used routinely in the NHS in England for the condition and population in the recommendations.

This is because there is not enough evidence to determine whether lifileucel is value for money in this population.

Why the committee made these recommendations

Usual treatment for previously treated unresectable or metastatic melanoma is ipilimumab, chemotherapy or best supportive care.

Lifileucel has not been directly compared in a clinical trial with usual treatment. The results of indirect comparisons with these treatments suggest that lifileucel increases how long people have before their condition gets worse and how long they live. But the results are very uncertain because of the methods used. There are also questions about how generalisable they are to NHS clinical practice.

There are also uncertainties in the economic model, including:

- the methods used for estimating long-term outcomes
- the costs used for setting up the service to provide lifileucel treatment, staff training and administration.

Because of the uncertainties in the clinical-effectiveness evidence and the economic model, it is not possible to determine the most likely cost-effectiveness estimates for lifileucel. So, lifileucel should not be used.

2 Information about lifileucel

Anticipated marketing authorisation indication

2.1 Lifileucel (Amtagvi, Iovance Biotherapeutics) does not have a marketing authorisation in the UK. The anticipated marketing authorisation for lifileucel is for the treatment of adult patients with unresectable or metastatic melanoma (Stage IIIc to Stage IV) previously treated with a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor.

Dosage in the marketing authorisation

2.2 The dosage schedule will be available in the summary of product characteristics for lifileucel.

Price

2.3 The list price of lifileucel is commercial in confidence, so cannot be reported here.

2.4 The company has a commercial arrangement, which would have applied if lifileucel had been recommended.

Carbon Reduction Plan

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for Iovance Biotherapeutics will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by Iovance Biotherapeutics, a review of this submission by the external assessment group (EAG) and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of condition

3.1 Melanoma is a cancer of the skin. Symptoms of unresectable or metastatic melanoma will depend on where the cancer has spread to. But general symptoms may include weight loss, muscle pain, confusion, memory problems, mood or personality changes, feeling sick and extreme fatigue. The patient experts explained that unresectable or metastatic melanoma has a significant effect on quality of life. They also described how people with melanoma live with the fear of progression, which has a major impact on mental wellbeing. The clinical experts explained that, in many people, the condition progresses after all available systemic treatments have been used. But these people are still fit enough to have further treatment. Without another treatment option, these people will eventually experience disease progression and death. The committee recognised the need for an effective treatment for previously treated unresectable or metastatic melanoma. It concluded that unresectable or metastatic melanoma has a significant impact on the quality of life for people with the condition.

Clinical management

Treatment pathway

3.2 First-line treatment options for unresectable or metastatic melanoma include PD-1 blocking antibodies (nivolumab, alone, with relatlimab or with ipilimumab, or, pembrolizumab alone). For people whose cancer is BRAF V600 mutation positive, a BRAF inhibitor, with or without a MEK

inhibitor, is also a treatment option, either first or second line. The clinical experts explained that treatment depends on tumour characteristics and patient and healthcare professional choice. But they added that most people would have a PD-1 blocking antibody, either alone or in combination, as first-line treatment. The committee agreed that it was in line with the treatment pathway for unresectable or metastatic melanoma in NHS clinical practice to position lifileucel:

- at second line, after a PD-1 blocking antibody
- at third line after a BRAF inhibitor, with or without a MEK inhibitor, if the cancer is BRAF V600 mutation positive.

Lifileucel

3.3 Lifileucel is a one-off single-dose tumour-infiltrating lymphocyte (TIL) cell therapy. TILs are immune cells that naturally target and destroy tumour cells. The company explained that lifileucel is made using cells from the tumour of the person that will have the treatment. After the cells have been collected, they are sent to a manufacturing site where they are multiplied into billions of cells. The product is then sent back to the hospital as a cryopreserved product. The company explained that lifileucel is administered in a 3-step process for which people need to be admitted to hospital. Before lifileucel is infused, people have lymphodepleting chemotherapy to prepare the body for the TIL cell therapy and to eliminate any suppressive cells. After lifileucel is infused, people have high-dose interleukin-2 to improve the chances of the TIL cells surviving in the body.

Comparators

3.4 The company submission compared lifileucel with ipilimumab, chemotherapy and best supportive care (BSC), which aligned with the NICE final scope. The clinical experts were supportive of the choice of comparators. They explained that, at second line (or third line if the cancer is BRAF V600 mutation positive), most people will have BSC. But a smaller proportion of people will not have had ipilimumab at earlier lines of

treatment (with a PD-1 blocking antibody), so would instead have ipilimumab. The clinical experts explained that chemotherapy is not often offered because, compared with BSC, it is not thought to provide any significant advantages. But they explained that some people choose to have chemotherapy. The committee agreed that ipilimumab, chemotherapy and BSC are appropriate comparators for people with previously treated unresectable or metastatic melanoma.

Clinical effectiveness

Study C-144-01

3.5 The clinical evidence for lifileucel came from C-144-01, an ongoing phase 2 open-label single-arm trial. It recruited people with unresectable or metastatic melanoma who had had 1 or more systemic treatments, including a PD-1-blocking antibody and, if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor. The company provided data from the June 2023 data cut, in which the median follow up for key efficacy outcomes was 27.6 months. The company explained that a later data cut was available, which was not presented in its submission. The study had 4 cohorts:

- cohort 1: people who had non-cryopreserved lifileucel
- cohort 2 and 4: people who had cryopreserved lifileucel
- cohort 3: people who had retreatment with lifileucel.

The company said that only data from cohorts 2 and 4 should be considered because non-cryopreserved lifileucel is not in clinical use and lifileucel's license will not include retreatment. It explained that cohorts 2 and 4 had the same eligibility criteria, and used the same lifileucel manufacturing process and treatment regimen, but enrolled people over different timeframes. The company used data from cohorts 2 and 4 to generate the pooled analysis set, which was used in its economic model. The EAG noted that there were differences in the

baseline characteristics between cohorts 2 and 4. Cohort 4 included a higher proportion of people with stage 4 melanoma, more than 3 lesions, elevated lactate dehydrogenase (LDH) levels, and liver or brain metastasis. It also said that people in cohort 4 had nearly twice the cumulative duration of prior anti-PD-1 treatment. The EAG explained that treating the melanoma in cohort 4 might have been more challenging than in cohort 2. But, despite the differences between the cohorts, the EAG thought that pooling the data was reasonable. The company said that the population in C-144-01 may have had more treatment before lifileucel than the population who would have lifileucel in NHS clinical practice. The clinical experts thought that, despite the possible differences in the level of pretreatment, the pooled population in C-144-01 would be generalisable to the population that would have lifileucel in the NHS.

The committee agreed that cohorts 2 and 4 were the relevant cohorts from C-144-01 to consider, so pooling the data from these may be reasonable. It also noted that pooling the cohorts resulted in a larger sample size, which is a benefit, especially because the data is used in indirect treatment comparisons (ITCs; see section 3.6). But the committee raised concerns that the median overall survival (OS) was substantially better in cohort 2 than cohort 4. This suggests that the presence of negative prognostic factors in cohort 4 had a substantial impact on the effectiveness of lifileucel. It was also aware that cohort 4 was the primary evidence used as the basis for lifileucel's Food and Drug Administration marketing authorisation application. The committee noted that the differences between cohorts resulted in uncertainty when interpreting the pooled analysis set. So, it requested the following further analyses:

- an explanation for why the baseline characteristics were different between the 2 cohorts when the eligibility criteria were the same

- a scenario analysis using only the latest data cut from cohort 4 in the ITCs and economic model, to help understand the impact of uncertainty when using the pooled analysis set
- further evidence on the generalisability of the pooled analysis set to the population who would have lifileucel in NHS clinical practice, considering the difference in baseline characteristics between the 2 cohorts
- outcomes for the pooled analysis set using the latest data cut.

ITCs

3.6 Because there were no trials directly comparing lifileucel with comparators, ITCs were needed for this comparison. To develop comparative clinical-effectiveness data, the company did:

- a simulated treatment comparison (STC) to compare lifileucel with ipilimumab (see section 3.7)
- a naive comparison to compare lifileucel with chemotherapy (see section 3.8).

STC compared with ipilimumab

3.7 The company did an STC using data from da Silva et al. (2021) for ipilimumab and data from the pooled analysis set of C-144-01 (see section 3.5) for lifileucel. Da Silva et al. was a retrospective cohort study in people with unresectable metastatic melanoma who had had anti-PD-L1 alone. It compared ipilimumab plus anti-PD-L1 (n=193) with ipilimumab (n=162). The median follow up was 22.1 months. The company thought that an STC could allow the relative effect of lifileucel compared with ipilimumab to be estimated. The STC used a model fitted to individual patient-level data (IPD) from C-144-01, adjusting for key prognostic factors to predict survival probabilities. The prognostic factors adjusted for in the company's STC were age, sex, disease stage, Eastern Cooperative Oncology Group score, LDH level and BRAF mutation status. Patient characteristics from da Silva et al. were then put into the model to get

predicted survival probabilities. These were used to generate adjusted Kaplan–Meier curves and pseudo-IPD for a population that had lifileucel but had the same characteristics as the da Silva et al. population. STC-adjusted hazard ratios were then calculated by comparing the generated pseudo-IPD with pseudo-IPD from da Silva et al. The results of the STC are considered confidential by the company, so cannot be reported here.

The EAG explained that it had some concerns about the robustness of the STC. Firstly, the results were highly dependent on whether LDH was included as a covariate. It also explained that the company had not adjusted for some prognostic factors and effect modifiers, such as target lesion sum diameter and line of treatment, which could have introduced bias. Finally, the EAG noted that the STC estimated a relative treatment effect in the da Silva et al. population. So, it was unclear whether the relative effect would be applicable to the population that would have lifileucel in the NHS. Overall, the EAG thought that the results of the STC should be interpreted with caution. The clinical experts explained that the presence of brain or liver metastases is a known negative prognostic factor. The committee requested that the STC be updated to adjust for any imbalance in the presence of brain or liver metastases between da Silva et al. and C-144-01. The committee concluded that, in the absence of trials directly comparing lifileucel with ipilimumab, an ITC was appropriate. It thought that the results of the company's STC were associated with uncertainty and concluded that it would take this into account in its decision making.

Naive comparison compared with chemotherapy

3.8 The company also did a naive comparison to compare lifileucel with chemotherapy. The clinical evidence for chemotherapy came from Mangin et al. (2021). This was a retrospective cohort study in people with unresectable stage 3 or 4 metastatic melanoma who had dacarbazine (n=28), temozolomide (n=21) and fotemustine (n=1). People had

previously had first-line treatment with an immune checkpoint inhibitor (pembrolizumab, nivolumab, ipilimumab) or a BRAF inhibitor with or without a MEK inhibitor. The company said that Mangin et al. was selected because:

- the chemotherapy regimens used reflected those listed in the NICE final scope
- the inclusion criteria were similar to those in C-144-01.

The company explained that a naive unadjusted ITC was done because the small sample size from Mangin et al. (n=50) meant that a population-adjusted ITC would result in uncertainty. The company and EAG noted that there were several differences in the baseline characteristics between Mangin et al. and C-144-01. The EAG explained that the naive unadjusted comparison failed to account for the population in Mangin et al. being less fit than the population in C-144-01. The EAG thought that, if a population-adjusted comparison could have been done, the relative efficacy would have been smaller than was seen in the naive unadjusted comparison. So, it explained that using the naive unadjusted comparison was likely to have resulted in optimistic relative efficacy estimates for lifileucel compared with chemotherapy.

The committee noted that the hazard ratios from the naive comparison of lifileucel with chemotherapy were similar to the STC-adjusted hazard ratios for the comparison of lifileucel with ipilimumab. The hazard ratios are considered confidential by the company, so cannot be reported here. The committee recalled that clinical experts had said that they would expect chemotherapy to be less effective than ipilimumab. So, the committee thought that the results of the naive comparison lacked face validity and should be interpreted with caution. It noted that a population-adjusted ITC was not suitable. So, it concluded, that, in the absence of any other data, the naive comparison should be used to

estimate the relative efficacy of chemotherapy. But, because the Mangin et al. population was less fit than the population in C-144-01, it thought that the relative efficacy estimates were optimistic. The committee concluded that it would take this into account in its decision making.

Economic model

Company's modelling approach

3.9 To estimate the cost effectiveness of lifileucel, the company presented a partitioned survival model with 3 health states: progression free, progressed disease and death. The model used a lifetime time horizon. It also included a decision tree for the lifileucel arm. This governed whether, after tumour harvest, people:

- stopped treatment before the infusion
- died before the infusion
- had an infusion that was out-of-specification
- had an infusion that met lifileucel's summary of product characteristics specifications.

Only people in the last group were assigned the costs and outcomes associated with lifileucel. People who stopped before an infusion or had an infusion out-of-specification were assigned part of the lifileucel treatment costs. But outcomes were derived from an estimated market-share-based weighting of ipilimumab, chemotherapy and BSC outcomes. The committee concluded that the company's model structure, and the assumptions for people who stopped treatment before an infusion or had an out-of-specification infusion, were suitable for decision making.

Selection for the lifileucel mixture cure model

3.10 The company used a mixture cure model (MCM) to model progression-free survival (PFS) and OS for lifileucel. The MCM assumed that there were 2 groups:

- people whose melanoma is cured immediately after having lifileucel and who will have a long-term survival similar to people without melanoma of the same age and sex
- people whose melanoma is not cured, and who have a continued risk of progression and death because of it.

The MCMs estimated a cure fraction that represented the proportion of people who were in the first group. The company said that using an MCM was supported by an observed plateau in C-144-01's PFS and OS Kaplan–Meier curves. The company's clinical experts said that people whose melanoma has not progressed after 3 years are assumed to have a long-term survival similar to the general population. The company selected an exponential MCM for OS. It said that the exponential MCM provided the best statistical fit and was clinically intuitive because it assumed that people whose melanoma is uncured die at a constant rate. The company selected a log-normal MCM for PFS, informed by clinical expert opinion.

The EAG thought that using MCMs to model PFS and OS for the lifileucel group was appropriate. But the EAG preferred to use a log-logistic MCM for both OS and PFS. It explained that the log-logistic MCM for OS produced a cure fraction that more closely aligned with the cure fraction suggested by the company's clinical experts. The EAG noted that the company's preferred MCMs resulted in a larger difference in the cure fractions for PFS and OS compared with its preferred MCMs. The EAG explained that you would only expect the cure fraction for OS to be higher than the cure fraction for PFS if there were effective treatments after progression. It noted that this was not

the case for people with previously treated unresectable or metastatic melanoma. But the clinical experts suggested that a difference in OS and PFS cure fractions was plausible. The clinical experts explained that a difference in OS and PFS cure fractions has been seen in clinical trials for other treatments. They explained that progression could include localised progression that could be treated in a way that does not affect the potential for a cure. They further explained that some melanoma treated with immunotherapies has been known to progress but then respond, which is known as pseudoprogression. The company said that data on PFS at subsequent treatment lines (PFS2) and data from a more recent C-144-01 data cut would support a higher cure fraction for OS than PFS. The committee agreed that further data may help resolve this uncertainty. It requested that the company provide additional analysis from C-144-01, outlining how this data justifies a higher cure fraction for OS than PFS, including:

- the most recent data cut
- PFS2 data
- the proportion having surgical resection after lifileucel.

Lifileucel and ipilimumab PFS and OS extrapolations

3.11 For its comparison of lifileucel with ipilimumab, the company applied the ratio of adjusted and unadjusted hazard ratios from the STC (see section 3.7) to the lifileucel MCMs (see section 3.10). It did this to estimate absolute OS and PFS outcomes for people who has lifileucel in the da Silva et al. (2021) population. The company used standard parametric models fitted directly to data from da Silva et al. to estimate absolute outcomes for people who had ipilimumab. It said that the short follow-up time in da Silva et al. meant that the standard parametric modelling approach was appropriate for outcomes in the ipilimumab arm, but that an MCM approach was not. But the company's clinical experts suggested that some people who have ipilimumab survive in the long term and their melanoma is considered to be cured. The company accounted

for this by assuming that people who had ipilimumab and were progression free after 3 years had long-term survival similar to people without melanoma of the same age and sex.

The EAG explained that the company's approach to estimating absolute outcomes for people who had lifileucel uplifted the OS and PFS cure fractions compared with the MCM. It noted that the implied cure fractions for lifileucel after adjustment far exceeded the cure fractions suggested by the company's clinical experts. The EAG preferred to use the unadjusted MCMs (see section 3.10) to estimate absolute outcomes for people who had lifileucel. The EAG applied the inverse of the adjusted hazard ratios from the STC to the lifileucel MCMs to estimate absolute outcomes for people who had ipilimumab. The EAG noted that the 3-year OS cure assumption applied in the company's model resulted in a very small proportion of people surviving in the long term with ipilimumab. The exact percentage is considered confidential by the company, so cannot be reported here. The EAG explained that its preferred approach resulted in a plateau in model-predicted ipilimumab OS and PFS. This suggested long-term survival for a small, yet slightly higher, proportion of people.

The committee noted that the company used unadjusted MCMs to estimate lifileucel's treatment effect when compared with chemotherapy and BSC. So, it thought that it was more appropriate to also use unadjusted MCMs for the comparison with ipilimumab. This meant that the absolute outcomes for lifileucel were the same for all of the comparisons. It also noted that the company did not provide any evidence to support the uplifted cure fractions associated with its preferred approach. These were higher than both the cure fractions suggested by its clinical experts and those estimated from the unadjusted models. The committee noted that it was unclear whether C-144-01 or the da Silva et al. population more closely reflected the population who would have lifileucel in NHS practice (see section 3.5). So, it was also unclear whether using the unadjusted

MCMs or adjustments from the STC based on the da Silva et al. population estimated the efficacy of lifileucel in a more relevant population. The committee concluded that using MCMs to estimate the long-term survival outcomes for lifileucel and ipilimumab was appropriate. It also concluded that the EAG's approach to modelling relative and absolute treatment effects for lifileucel compared with ipilimumab was more appropriate than the company's approach. But the committee acknowledged the most appropriate approach may change when data with more complete follow up (see section 3.5) is considered.

Chemotherapy and BSC PFS and OS extrapolations

3.12 The company fitted standard parametric survival curves to data from the chemotherapy arm in Mangin et al. (2021; see section 3.8) to estimate long-term PFS and OS for people who had chemotherapy in the model. The EAG noted that all the standard parametric models for PFS provided a poor visual fit to the observed data. It further noted that several of the standard parametric survival models did not reflect the observed hazards. The EAG thought that more flexible parametric models, such as spline models, may better reflect the observed hazards. The company said that its systematic literature review did not identify any suitable and up-to-date data sources for BSC. So, the company chose to use data from people who had chemotherapy in Mangin et al. as a proxy. It modelled absolute OS and PFS outcomes for people who had BSC by applying a hazard ratio of 2.0 to the modelled outcomes for chemotherapy. The company explained that it chose a hazard ratio of 2.0 because its clinical experts thought that BSC survival outcomes are about 50% worse than the chemotherapy outcomes.

The EAG preferred to assume that outcomes for BSC and chemotherapy are equivalent because this is what its clinical experts said they would expect. It further explained that the minutes from the company's advisory board meeting stated that some of the company's clinical experts thought that chemotherapy provides no advantage over BSC. The clinical experts

at the meeting explained that BSC is thought to be as effective as chemotherapy, which is only offered when someone's preference is to continue having anticancer therapy. The committee recalled that estimates based on Mangin et al. were likely to underestimate the effect of chemotherapy seen in the population having treatment in clinical practice (see section 3.8). So, using this data was likely to result in optimistic relative efficacy estimates for lifileucel compared with chemotherapy in the model. The committee also agreed that it was reasonable to assume BSC and chemotherapy are equally effective. But, because the same data was used for BSC as for chemotherapy, the same uncertainties associated with estimating the effectiveness of chemotherapy also applied to the BSC estimates. The committee concluded that it would take this into account in its decision making.

Utility values

Source of utility values

3.13 Health-related quality-of-life data was collected in C-144-01 using the EORTC QLQ-C30 questionnaire. The company used the Kim et al. (2012) and the Wojciechowski et al. (2023) models to approximate EQ-5D scores. But the company could not use these values in its model. It explained that the quality-of-life data was only an exploratory outcome, and the sample size was small. So, it was unable to determine utility value changes over time. It further explained that the missing data was not random. This could have affected the statistical reliability of mapped utilities, and the mapping models identified were not developed based on UK demographics. Instead, the company extracted utility values from the published literature and 10 previous NICE technology appraisals (progression free: 0.77, progressed disease: 0.67).

The EAG explained that the company's approach was unconventional and that it had some concerns. Firstly, clinical experts at the company's advisory board said that they would have expected a larger gap between

progression-free and progressed-disease utility values. The EAG also explained that some of the utility values were not derived using the EQ-5D measurement method as specified in the NICE reference case. But it noted that the company had presented multiple sensitivity analyses. These included analyses using the source with the largest difference between progression-free and progressed-disease utility values and excluding non-EQ-5D values. The EAG explained that the sensitivity analysis had a small impact on the cost-effectiveness estimates. The committee emphasised that, ideally, health-related quality-of-life data should be collected for people in the relevant clinical trial using EQ-5D. But the committee noted that NICE's health technology evaluations manual states that, if EQ-5D data is not available from the relevant trials, it can be sourced from the literature. The committee was satisfied that EQ-5D data was not available from the relevant clinical trial. It also thought that the company had provided sensitive analyses that shows that the choice of data set has a small impact on the cost-effectiveness estimates. The committee concluded that the company's analysis which excluded non-EQ-5D values should be used for decision making.

Costs

Set-up, logistics, training and delivery costs

3.14 The company's base-case model included administration costs associated with lifileucel infusion, and pretreatment and post-treatment costs, specifically:

- tumour tissue procurement
- lymphodepletion chemotherapy administration
- lifileucel administration
- interleukin-2 administration and monitoring.

The EAG explained that set-up, training and logistics costs associated with introducing lifileucel into the NHS were not included in the

company's base-case model. The EAG used the NHS England's CAR-T tariff (£60,863) to account for these costs. To avoid double counting for people who had lifileucel, it removed the costs associated with lifileucel administration listed above, the adverse event management costs and the health-state costs for the first 100 days. NHS England explained that these costs are also covered by the CAR-T tariff. It also explained that there is limited evidence for what the associated costs for lifileucel will be. It said that, to give providers certainty about income in the implementation phase, it is committed to commissioning lifileucel activity in line with the cost of the CAR-T tariff. So, it thinks that the CAR-T tariff should be incorporated into the evaluation. NHS England also thought that some costs in the CAR-T tariff would not apply for lifileucel but that this would be offset by costs which would apply but are not captured in the tariff.

The company thought that its model captured the relevant administration costs, and that modelled hospitalisation costs after lifileucel administration were conservative. It said that hospitals which provide lifileucel will have existing cell therapy capabilities, so should not need additional staff. It also said that it provides hospitals with training at no cost. The company explained that it was uncertain exactly what costs made up the CAR-T tariff. But it thought that the tariff likely included costs that either:

- were not relevant for lifileucel (such as leukapheresis), or
- were already included in the model and not appropriately removed in the EAG's analysis (such as monitoring after discharge, adverse event management and hospitalisation).

The clinical experts at the meeting agreed that some of the common complications seen in CAR-T therapies are not seen with lifileucel. They also agreed that the company's assumptions for the amount of

time spent in the intensive care unit may have been higher than expected in clinical practice. The company explained that the true resource use for lifileucel was likely somewhere between the costs included in the company's and the EAG's model. The committee recognised that the company had provided justification for the resource use costs that were included in its model. But it was uncertain whether there were any set-up, training or delivery costs that had not been included. It requested that NHS England provides further details on what is included in the CAR-T tariff that is not already covered by the company's resource use estimates. It also requested that the company provide further analyses on how its resource use estimates are reflective of those that will be incurred in the NHS, including for the set-up, logistics and training associated with lifileucel.

Severity

3.15 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to QALYs (quality-adjust life years; a severity modifier) if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates in line with NICE's health technology evaluations manual. In the company's base case, the proportional QALY shortfall was 96.1% for chemotherapy, 98.0% for BSC and 93.4% for ipilimumab. In line with NICE's health technology evaluations manual, the calculated proportional QALY shortfalls resulted in a QALY weight of 1.7 for chemotherapy and BSC and 1.2 for ipilimumab. The committee noted that the QALY shortfall estimates for chemotherapy and BSC were based on data from Mangin et al. (2021). It thought these underestimated the effect of chemotherapy that would be seen in the population treated in NHS clinical practice (see section 3.8). The committee concluded that the severity weight of 1.7 applied to the QALYs for the comparisons with chemotherapy and BSC was appropriate, but uncertain, based on the data presented to it. It further concluded that

the severity weight of 1.2 applied to the QALYs for the comparison with ipilimumab was appropriate. But the committee acknowledged that the appropriate severity weights may may change after consideration of the further analysis it has requested (see section 3.16).

Cost-effectiveness estimates

Committee's requests for further analyses and preferred assumptions

3.16 The committee noted there was uncertainty associated with many of the model inputs and requested the following further analyses:

- an explanation for why the baseline characteristics were different between the 2 cohorts when the eligibility criteria were the same (see section 3.5)
- a scenario analysis, using only the latest data cut from cohort 4 in the ITCs and economic model, to help understand the impact of uncertainty when using the pooled analysis set (see section 3.6)
- further evidence on the generalisability of the pooled analysis set to the population who would have lifileucel in NHS clinical practice, considering the difference in baseline characteristics between the 2 cohorts (see section 3.5)
- outcomes for the pooled analysis set using the latest data cut (see section 3.5)
- an analysis from C-144-01, outlining how this data justifies a higher cure fraction for OS than PFS (see section 3.10), including:
  - the most recent data cut
  - PFS2 data
  - the proportion undergoing surgical resection after lifileucel
- further details on what is included in the CAR-T tariff that is not already covered by the company's resource use estimates (from NHS England) (see section 3.14)
- further analyses on how its resource use estimates are reflective of those that will be incurred in the NHS, including for the set-up, logistics

and training associated with lifileucel (from the company; see section 3.14)

- an analysis that resolves the problems the EAG identified in the company's probabilistic analysis.

The committee discussed its preferred assumptions, noting that these may change after consideration of the further analyses it has requested. But, given the data it was presented, its preferred assumptions included:

- ipilimumab, chemotherapy and BSC included as relevant comparators (see section 3.4)
- estimating the relative efficacy of chemotherapy using the naive comparison of C-144-01 and Mangin et al. (2021; see section 3.8)
- using a log-logistic MCM for extrapolating lifileucel PFS and OS (see section 3.10)
- estimating OS and PFS for lifileucel using unadjusted MCMs (see section 3.11)
- estimating OS and PFS for ipilimumab by applying the inverse of the STC-adjusted hazard ratios to the lifileucel MCMs (see section 3.11)
- using chemotherapy as a proxy for BSC and assuming both treatments are equally effective (see section 3.12)
- using utility values from the analysis that excluded non-EQ-5D values (see section 3.13)
- applying a severity weight of 1.7 to the comparisons with chemotherapy and BSC (see section 3.15)
- applying a severity weight of 1.2 to the comparison with ipilimumab (see section 3.15).

The committee noted that the costs associated with the set-up, logistics, training and delivery of lifileucel were uncertain (see section 3.14). The committee also noted the following additional

differences between the company and the EAG's base-case analysis, which it noted had a minimal impact on the incremental cost-effectiveness ratio (ICER):

- using an assumed cure time point of 5 years
- tumour procurement costs weighted using data on the distribution of resection sites from C-144-01.

Because of confidential discounts for lifileucel and comparators, exact ICERs are confidential, so cannot be reported here. The committee was unable to agree on its preferred ICER because further analysis is likely to affect its preferred assumptions. But the committee noted that, including the commercial discounts, all the cost-effectiveness estimates presented were substantially higher than what NICE considers a cost-effective use of NHS resources. This included both the company's and EAG's cost-effectiveness estimates.

Acceptable ICER

3.17 NICE's manual on health technology evaluations notes that, above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty, specifically around the:

- generalisability of the C-144-01 cohorts (see section 3.5)
- STC used to compare lifileucel with ipilimumab (see section 3.7)
- absolute treatment effects for lifileucel compared with ipilimumab (see section 3.11)
- use of a naive comparison to compare lifileucel with chemotherapy (see section 3.8)

- relative treatment effects for lifileucel compared with BSC (see section 3.12)
- whether the company's approach captures all resource costs that are relevant for the evaluation (see section 3.14).

The committee thought that the additional requests for analyses (see section 3.16) may mitigate some of the outstanding uncertainty. So, the committee concluded that it could not yet determine an acceptable ICER threshold.

Other factors

Equality

3.18 Several equalities issues were identified by stakeholders, including that:

- some people may not be able to easily get to a treatment centre
- the suitability of lifileucel for people with a learning or physical disability will need to be considered carefully to ensure it would be offered when appropriate
- lifileucel is unsuitable for women, trans men and non-binary people who are pregnant
- lifileucel is unsuitable for some older, frailer people
- C-144-01 did not include people under 18 years.

The committee noted that access to specialist centres is an implementation issue that cannot be addressed by a NICE evaluation recommendation. Disability, pregnancy and age are protected characteristics under the Equality Act 2010. But, because its recommendation does not restrict access to treatment for some people over others, the committee agreed the recommendation did not lead to any equalities issues.

Conclusion

Recommendation

3.19 The committee noted the uncertainties associated with many of the model inputs, including the survival estimates and costs. The committee was unable to agree upon its preferred ICER because of the uncertainties. So, lifileucel should not be used for previously treated unresectable or metastatic melanoma (Stage IIIc to Stage IV) in adults who have had:

- a PD-1 blocking antibody, and
- a BRAF inhibitor with or without a MEK inhibitor if the cancer is BRAF V600 mutation positive.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Radha Todd

Chair, technology appraisal committee A

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a principal technical adviser, a project manager and an associate director.

Ross Wilkinson
Technical lead

Albany Chandler
Technical adviser

Lizzie Walker
Principal technical adviser

Jennifer Upton
Project manager

Ian Watson
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