National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Lifileucel for previously treated unresectable or metastatic melanoma [ID3863]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Iovance Biotherapeutics (company)	It is appropriate to refer lifileucel to NICE for single technology appraisal.	Thank you for your comment. No action required
	Melanoma Focus	This is an appropriate therapy to evaluate given the unmet need of the patient population in question	Thank you for your comment. No action required
Wording	Iovance Biotherapeutics (company)	The wording of the draft remit which references appraising the clinical and cost-effectiveness of lifileucel is appropriate and aligned with both the anticipated marketing authorisation and use of lifileucel within clinical practice in England and Wales.	Thank you for your comment. No action required
	Melanoma Focus	The wording is acceptable for the evaluation objective	Thank you for your comment. No action required

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Timing Issues	Iovance Biotherapeutics (company)	This appraisal should be initiated as soon as possible. As reported in 'Appendix B – Draft Scope', there were 12,477 registrations of newly diagnosed cases of malignant melanoma of the skin in England in 2020. In the same year, 2,010 deaths with malignant melanoma of the skin as the underlying cause were recorded in England. The unresectable or metastatic nature of the condition means that it is difficult to treat, with high rates of progression after prior standard of care and it is unlikely patients may be cured of their cancer. Lifileucel will be appraised in patients who have already received at least one prior line of therapy (previously treated with a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor). Current systemic treatment options for these patients include ipilimumab and chemotherapy1. However, ipilimumab may have been used already in 1L as part of the ipilimumab/nivolumab combination and in these cases would not be an option in 2L+, and chemotherapy has both poor evidence of treatment response and poor durability of response2,11. Therefore, there is a high unmet need for a well-tolerated treatment with proven efficacy in this patient population, meaning this evaluation should be initiated as soon as possible.	Thank you for your comment. The appraisal will follow scheduled timelines. No action required
	Melanoma Focus	There is a patient population who may potentially benefit from this therapy who are currently without meaningful treatment options therefore there is a need to proceed to review without undue delay	Thank you for your comment. The appraisal will follow scheduled timelines. No action required

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft remit		No comments	

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Iovance Biotherapeutics (company)	The Company generally agrees that the background information gives a reasonable summary of clinical practice for unresectable or metastatic melanoma. While several immunotherapy and targeted therapy options are recommended by NICE, the proposed indication for lifileucel is after previous treatment of both of these modalities. Additionally, NICE does not recommend use of anti-PD-1 treatments or BRAF/MEK therapies after progression on said agents, which is the basis for the Company's rationale to exclude the majority of the options in this scoping document as comparators to lifileucel.[3] This is detailed below in the comparator section and is important to note as part of the background information.	Thank you for your comment. The scope is intended to be a broad overview of the topic. The comment concerning the choice of comparators is addressed in the comparator section below. No action required.
	Melanoma Focus	The background information is acceptable in its content overall but very disjointed in its presentation and layout. This may be challenging for stakeholders without exacting specialist knowledge to follow. This should be considered when assessing responses to this scoping document. There is also no comment on the overall effectiveness of therapy strategies in each section nor any mention on the duration of response which can be expected – which is important to understand to then be able to understand the extent of	Thank you for your comment. The scope is intended to be a broad overview of the topic. NICE's guidance on nivolumab-relatlimab

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		the unmet need. There is no comment on nivolumab-relatlimab for melanoma which is now available.	has been added to the background section.
Population	Iovance Biotherapeutics (company)	The wording of the population is aligned with both the anticipated UK marketing authorisation and use of lifileucel within clinical practice in England and Wales: **adults with previously treated unresectable or metastatic melanoma.**	Thank you for your comment. No action required
	Melanoma Focus	Overall – yes, acceptable	Thank you for your comment. No action required
Subgroups	Iovance Biotherapeutics (company)	The Company agrees with the inclusion of BRAF V600 mutation status as a subgroup as this criterion is anticipated to be included in the UK marketing authorisation. Furthermore, BRAF V600 mutation status is a key factor in defining the treatment pathway of unresectable or metastatic melanoma patients in the UK. This reflects the treatment pathway in the UK with BRAF status defining whether patients receive treatment with a BRAF inhibitor with or without a MEK inhibitor.1,2 Nevertheless it is important to clarify that lifileucel demonstrated compelling efficacy outcomes, regardless of BRAF mutation status, with an ORR 31.7% of for BRAFmut (after failure of prior therapy with a BRAF inhibitor with or without a MEK inhibitor) and 31.3% for BRAFwt.4 Both BRAFmut and BRAFwt patients were also previously treated with anti-PD-1 inhibitors. However, the Company does not agree with the inclusion of programmed death ligand 1 (PD-L1) expression status as a subgroup. There is little evidence that PD-L1 expression is routinely tested for in UK clinical practice in patients with metastatic melanoma (as heard in NICE TA400), highlighting	Thank you for your comment. PD-L1 expression status has been removed as a subgroup.

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		that it is not a key biomarker for clinicians. The Company has consulted with UK clinical KOLs managing patients with melanoma, to inform the lifileucel UK HTA decision problem, and the clinicians agreed that PD-L1 expression testing does not happen often in practice.5 Furthermore, there is little evidence that PD-L1 expression status is a key prognostic factor in advanced melanoma.6,7 In fact, a “meta-analysis of studies that enrolled 1062 patients demonstrated that high PD-L1 expression was not associated with poor prognosis in patients with melanoma. In addition, PD-L1 expression remained a non-significant prognostic factor in various subgroups of OS and PFS”.6 Furthermore, in the previous NICE TA400 the committee went on to conclude that PD-L1 expression is not appropriate to base recommendations on in advanced melanoma.8 The C-144-01 trial studying lifileucel demonstrated there was no significant difference in the ORR by PD-L1 expression status, with less than a 3% difference in ORR in patients with tumour proportion score ≥5% vs. <5%.9 As such there is no relevance of a PD-L1 expression status subgroup. Overall, PD-L1 expression status should be removed as a potential subgroup from the NICE scope, given the lack of prognostic value of PD-L1 expression status and the irrelevance of anti-PD-1 treatments within the lifileucel decision problem. The Company would like to clarify that the currently recommended immune checkpoint inhibitors, Pembrolizumab and Nivolumab, are anti-PD-1 inhibitors (rather than anti-PD-L1 inhibitors). Based on the TA's referenced in this scoping document, only anti-PD-1 inhibitors are recommended to treat advanced melanoma.	
	Melanoma Focus	Patients with mutant and wildtype disease can potentially benefit equally from the therapy but the positioning of therapy for the mutant patients can be challenging as it requires progression and the pace of disease at this point in a disease course can be rapid and preclude use of an effective option.	Thank you for your comment. NICE can only appraise a treatment within its marketing authorisation,

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		Consideration of where in the treatment pathway this product is used should be carefully considered for maximal efficacy and outcome.	which may determine where it is placed in the treatment pathway. No action required.
Comparators	Iovance Biotherapeutics (company)	The Company has major concerns over the relevance of the treatments outlined in the comparator list and disputes the inclusion of: • Anti-PD-1 treatments (nivolumab with ipilimumab, nivolumab monotherapy, pembrolizumab monotherapy, pembrolizumab with ipilimumab) • BRAF+/-MEK inhibitors (encorafenib with binimetinib, trametinib with dabrafenib, dabrafenib monotherapy, vemurafenib monotherapy) • Talimogene laherparepvec (T-VEC) The proposed indication for lifileucel is for patients who have been previously treated with the anti-PD-1 treatments and BRAF+/-MEK inhibitors proposed by NICE. Since NICE does not recommend use of anti-PD-1s after progression, the Company proposes excluding (1) 'Anti-PD-1 treatments' from the draft scope. As with anti-PD-1 treatments, NICE does not recommend use of BRAF/MEK therapies after progression, so the Company proposes excluding (2) 'BRAF+/-MEK inhibitors' from the draft scope. The Company also proposes excluding (3) 'Talimogene laherparepvec', as there is little overlap between the two patient populations eligible for T-VEC, and T-	Thank you for your comments. In accordance with your comments, BRAF inhibitors with or without MEK inhibitors, anti-PD-1 treatments and talimogene laherparepvec have been removed as comparators from the scope. The following treatments have been added as comparators: • dacarbazine • temozolomide • paclitaxel • paclitaxel and carboplatin • best supportive care

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		VEC is not recommended for use in patients for whom systemically administered immunotherapies is not suitable. A more detailed explanation for the exclusion of treatments in lines 1, 2 and 3 are outlined below. <u>Anti-PD-1-based treatments in patients previously treated with a systemic therapy</u> The Company does not agree that anti-PD-1 treatments (nivolumab, pembrolizumab; either used as monotherapy or in combination) are relevant comparators. All lifileucel patients have been previously treated with an anti-PD-1 treatment, and retreatment is not reimbursed by the NHS or conducted in clinical practice in the UK. Published NICE guidance recommends treatment with an anti-PD-1 therapy in the first-line setting, if BRAF V600 wildtype.8,10–12 However, most patients receive nivolumab-ipilimumab combination therapy at first-line, regardless of BRAF mutation status.1,2 The UK clinical KOLs consulted by the Company agree that NICE recommended anti-PD-1 treatments are established as standard of care in UK clinical practice, with most patients expected to receive nivolumab-ipilimumab at first-line.5 Some patients would not be eligible for ipilimumab and may receive one of nivolumab with relatlimab or nivolumab monotherapy, in line with NICE guidance.1,10–12 UK clinical KOLs mentioned that these 1L ipilimumab-ineligible patients will also not receive ipilimumab in later lines. Note there is no NICE guidance on treatment with pembrolizumab in combination with ipilimumab for unresectable or metastatic melanoma – therefore this is not relevant for consideration as a comparator.	

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		Patients already treated with an anti-PD-1 treatment are no longer eligible to be retreated with the same or another anti-PD-1 treatment. This reflects what NHS reimburses in clinical practice, as outlined in the NHS England National Cancer Drugs Fund List document (October 2022).3 This was also confirmed by UK KOLs, who stated that they do not routinely have the option to retreat second-line plus unresectable or metastatic melanoma patients with an anti-PD-1, within the NHS, if they have already used an anti-PD-1 at first-line. The pivotal lifileucel trial (C-144-01) excluded any patients who had not previously received an anti-PD-(L)1 treatment and the UK marketing authorisation is expected to be consistent with this criteria.9 Given the NICE restrictions on retreatment with an anti-PD-1 and exclusion of 'non anti-PD-1 pretreated patients' from the lifileucel clinical evidence and anticipated UK marketing authorisation, the Company maintains that nivolumab with ipilimumab, nivolumab monotherapy, pembrolizumab monotherapy, pembrolizumab with ipilimumab should be removed from the final scope. <u>BRAF+/-MEK inhibitors in patients positive for BRAF V600 mutation</u> The Company does not agree BRAF inhibitors with or without MEK inhibitor are relevant comparators. All lifileucel patients positive for BRAF V600 mutation have been previously treated with a BRAF inhibitor with or without a MEK inhibitor, and retreatment is not reimbursed by the NHS or conducted in clinical practice.	

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		The Company agrees BRAF inhibitors with or without MEK inhibitor are established treatment for unresectable or metastatic melanoma in patients positive for BRAF V600 mutation. This is outlined in NICE guidance and also in the ESMO guidelines.1,2,15–18 There are a number of factors which define whether BRAF-mutation positive patients receive a BRAF+/-MEK inhibitor, such as rapid disease progression, brain metastases, elevated lactate dehydrogenase, patient fitness and contraindications for immunotherapy.1,2 This was also confirmed by UK clinical KOLs, who agreed that BRAF+/-MEK are established care for BRAF-mutation positive patients, but that it is usually used after front-line nivolumab-ipilimumab combination therapy.5 However, inclusion of BRAF+/-MEK inhibitors in the lifileucel scope is incorrect, for similar reasons as the anti-PD-1 treatment, since UK clinicians cannot retreat patients with a BRAF+/-MEK inhibitor. This reflects what NICE reimburses in clinical practice, as outlined in the NHS England National Cancer Drugs Fund List document (October 2022).3 This was also confirmed by UK KOLs, who stated that they do not routinely have the option within the NHS to retreat second-line plus positively mutated BRAF V600 metastatic melanoma patients, with an BRAF+/-MEK inhibitor if they have already used an BRAF+/-MEK inhibitor earlier in the treatment pathway.5 The pivotal lifileucel trial (C-144-01) excluded any patients who not had previously received an BRAF+/-MEK inhibitor (if BRAF V600 mutation positive). This exclusion is an addition to criteria on pretreatment with an anti PD-1 and the UK marketing authorisation is expected to be consistent with this criteria.9 Given the NICE restrictions on retreatment with a BRAF+/-MEK inhibitor and exclusion of non BRAF+/-MEK inhibitor pretreated patients from the lifileucel clinical evidence and UK marketing authorisation, the Company maintains that BRAF+/-MEKi such as encorafenib with binimetinib. trametinib	

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		with dabrafenib, dabrafenib monotherapy, vemurafenib monotherapy should be removed from the final scope. T-VEC (Talimogene laherparepvec) The Company does not agree that T-VEC is a relevant comparator for lifileucel. UK KOL opinion stated that T-VEC is rarely used and is not established care in clinical practice to treat unresectable or metastatic melanoma.5 A key reason for this is in the profile of patients eligible for T-VEC within the NICE recommendation, which excludes melanoma patients if the disease has spread to bone, brain, lung or other internal organs, and recommends treatment only to those in stage 3B, 3C or 4M1a .13 These criteria select patients with lower disease burden. Given the lifileucel C-144-01 trial criteria has no restrictions on disease burden, the population treated in C-144-01 is different from the population for whom T-VEC is indicated. This is evident in a comparison of disease characteristics in the C-144-01 trial and the key clinical trial for T-VEC, with the proportion of patients in the C-144-01 trial being more heavily pre-treated (line of therapy), at a later cancer stage (stage 4 vs. stage 3) and with higher levels of LDH (a key factor which is correlated with metastatic melanoma tumour burden).9,14 In summary most patients eligible for lifileucel would not be eligible for T-VEC, this is underpinned through the clinical evidence for both treatments, reflecting that T-VEC is designated for patients with lower disease burden and without metastasis to bone or visceral organs. NICE does recommend T-VEC for metastatic melanoma, however it is only in patients for which “treatment with systemically administered immunotherapies is not considered the best option by a multidisciplinary team".13 In practice this requires patients to be either ineligible for anti-PD-1 therapy first-line, or if treated with anti-PD-1 in first line, have a limited recurrence not involving the bone or brain, lung or other internal organs which is injectable with T-VEC. As such, the Company maintains that T-VEC should be removed from the final scope.	

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		List of relevant comparators for lifileucel for the treatment of adult patients with unresectable or metastatic melanoma in England and Wales The Company maintains that upon removal of the following comparators, for the reasons expressed above: anti-PD-1 at second line plus, targeted treatments at third line plus (if BRAF V600 mutation positive) and talimogene laherparepvec, the following treatments are relevant comparators for lifileucel: Chemotherapy (specifically dacarbazine), is recommended within the published NICE metastatic melanoma guidelines (2022) and confirmed with UK KOLs as a relevant treatment in patients second-line plus.1,5 Unlike for T-VEC, chemotherapy does not have criteria that excludes use for the majority of lifileucel-eligible patients. Ipilimumab monotherapy, as discussed above, is a relevant comparator for patients who have not received an anti-CTLA-4 first-line. This reflects NICE guidance, both in the NICE metastatic melanoma guidelines and aligns to the NICE TA950 committee conclusion for second-line plus therapy in untreated unresectable or metastatic melanoma.1,11 Ipilimumab was also confirmed as a relevant comparator by UK KOL opinion.5 However, the proportion of patients receiving ipilimumab monotherapy in second-line plus is not high for two reasons. As with anti-PD-1 antibodies, the NHS does not reimburse ipilimumab in successive lines of therapy.5 Given most patients receive nivolumab-ipilimumab in the first-line there is a sizeable proportion of patients ineligible for ipilimumab at second-line plus.5 Additionally, poor patient fitness can mean that few patients can tolerate the serious adverse events associated with ipilimumab, as based on UK KOL opinion.5 There is also evidence that ipilimumab monotherapy does not benefit patients with elevated	

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		LDH, making populations treated with 2L+ ipilimumab difficult to compare with the broad, targeted lifileucel population.19 Best supportive care (BSC), is a relevant comparator for patients. This reflects NICE guidance, both in the NICE metastatic melanoma guidelines and aligns with the NICE TA950 committee conclusion for second-line plus therapy in untreated unresectable or metastatic melanoma.1,11BSC was also confirmed as a relevant comparator by UK KOL opinion.5 The UK KOLs went further to define BSC as palliative care or end of life care, i.e. patients considered not sufficiently fit enough to receive systemic treatment	
	Melanoma Focus	The list is missing nivolumab-relatlimab which is available for the treatment of unresectable or metastatic melanoma.	Thank you for your comment. Nivolumab-relatlimab was recently recommended for treating previously untreated melanoma. Lifileucel is being assessed in people with previously treated melanoma, so nivolumab-relatlimab would not be considered an appropriate comparator for this appraisal. No action required.

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Outcomes	Iovance Biotherapeutics (company)	The Company agrees with the listed outcomes.	Thank you for your comment. No action required
	Melanoma Focus	Reasonable – adverse effects of treatment and QoL needs to take into account the procurement of the tissue required for study, not just the study product itself.	Thank you for your comment. The committee will consider all aspects of quality of life during the appraisal.
Equality and Diversity	Iovance Biotherapeutics (company)	There are no equality issues.	Thank you for your comment. No action required
	Melanoma Focus	Geographic deliverability of this therapy will need to be considered for equality of access. There is also a consideration to be made for TYA patients who may also benefit from this therapy as the behaviour of melanoma is the same in this patient group as it is in patients 18+ and they are often disadvantaged by failure to include in clinical trials.	Thank you for your comment. The committee will consider whether its recommendations could have a different impact on people protected by the equality legislation than on the wider population. The issues raised have been added to the equalities impact assessment (EIA).

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Other considerations	Iovance Biotherapeutics (company)	There are no additional issues to comment on.	Thank you for your comment. No action required
Questions for consultation	Iovance Biotherapeutics (company)	The Company would like to explore the candidacy of lifileucel for managed access and welcome discussions pertaining to commercial access agreements and managed access agreements (including via the cancer drugs fund). Lifileucel will be prescribed in secondary care with routine follow-up in secondary care. The Company considers that lifileucel will result in some substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation. Lifileucel is considered an innovative 'step-change' in the management of previously treated unresectable or metastatic melanoma as the first tumour-infiltrating lymphocyte therapy to be recommended in the treatment landscape (or in any condition in England and Wales). Lifileucel would introduce a new innovative treatment option, expanding treatment choice for melanoma patients and enabling greater patient autonomy and ability to make more tailored treatment decisions. As the administration of lifileucel is completed within a short treatment window (3-part regimen of non-myeloablative lymphodepletion, the one-time infusion of the lifileucel and a short-course of High Dose interleukin-2) lifileucel does not require frequent hospital visits as is the case with chemotherapies such as dacarbazine, which require intravenous	Thank you for your comment. The exploration of managed access will be highlighted with our commercial team. The committee will consider benefits that are unlikely to be included in the QALY calculation during the appraisal process.

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		administration, for 5 days every 3 weeks20 There is also no cumulative toxicity from repeated cycles of chemotherapy. This will lead to improvements in quality of life for patients and will also ease the burden on caregivers. These benefits related to expanded treatment choice and reduced burden of administration for patients and their caregivers might not be adequately captured by QALY calculations	
Additional comments on the draft scope		No comments	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Novartis

MSD