NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

APPEAL HEARING

# Advice on tebentafusp for treating advanced (unresectable of metastatic) uveal melanoma.

# Decision of the panel

## Introduction

1. An appeal panel was convened on 20 October 2023 to consider an appeal against NICE’s final draft guidance, to the NHS, on tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma [ID1441].
2. The appeal panel consisted of:

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| * Professor Jon Cohen
 | Chair |
| * Professor Gary Ford
 | Non-Executive Director (NICE) |
| * Professor Peter Groves
 | Health service representative |
| * Rachel Russell
 | Industry representative |
| * David Chandler
 | Lay representative |

1. None of the members of the appeal panel had any competing interest to declare.
2. The panel considered appeals submitted by Immunocore Ltd (Immunocore) and two patient groups, Melanoma Focus and OcuMel UK.
3. Immunocore was represented by:

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| * Chris Hoyle
 | Head of Market Access |
| * Mandy Turton
 | Medical Director |
| * Jasmine Farrington
 | HTA Specialist |
| * Aurelie Meunier
 | Health Economist |
| * Marie Manley
 | Legal Counsel |

1. Melanoma Focus was represented by:

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| * Dr Joe Sacco
 | Consultant Medical Oncologist (Clatterbridge Cancer Centre) |
| * Professor Mark Middleton
 | Professor of Experimental Cancer Medicine and Consultant Medical Oncologist (University of Oxford) |

1. OcuMel UK was represented by:

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| * Jo Gumbs
 | Ocumel UK CEO |
| * Victoria McMorran
 | Clinical Nurse Specialist |
| * Helen Evans
 | Patient representative |
| * Victoria Jones
 | Patient representative |
| * Professor Mark Middleton
 | Professor of Experimental Cancer Medicine and Consultant medical Oncologist (University of Oxford) |

1. In addition, the following individuals involved in the appraisal were present and available to answer questions from the appeal panel:

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| * Dr James Fotheringham
 | Vice Chair, technology appraisal committee A |
| * Dr Jacoline Bouvy
 | Programme director, NICE |
| * Janet Robertson
 | Associate director, NICE |
| * Dr Steve Edwards
 | Member, technology appraisal committee A |
| * Christian Griffiths
 | Health technology adviser, NICE |

1. The appeal panel’s legal adviser, Alistair Robertson (DAC Beachcroft LLP), was also present.
2. The appeal panel is grateful to both Helen Evans and Victoria Jones, both of whom gave moving evidence of the experience of those living with uveal melanoma. Victoria Jones talked of her personal experience of the effect of tebentafusp, which she had been taking as part of a clinical trial.
3. Under NICE’s appeal procedures, members of the public are admitted to observe appeal hearings and several members of the public and NICE staff observed the proceedings which were held via Zoom.
4. This decision letter sets out the grounds of appeal in the order in which they were heard by the panel during the appeal hearing. Some appeal grounds heard by the panel considered similar matters. Where appropriate, the panel have explained their rationale for upholding / dismissing similar appeal points together.
5. There are two grounds under which an appeal can be lodged:

Ground One: In making the assessment that preceded the recommendation, NICE has:

(a) Failed to act fairly; and/or

(b) Exceeded its powers.

Ground Two: The recommendation is unreasonable in light of the evidence submitted to NICE.

1. Dr Mark Chakravarty, NICE Lead non-executive director for appeals, in preliminary correspondence had confirmed that:
* Immunocore had potentially valid grounds of appeal under Grounds 1a and 2,
* OcuMel UK had potentially valid grounds of appeal under Ground 2; and
* Melanoma Focus had potentially valid grounds of appeal under Ground 2.
1. The appraisal that is the subject of the current appeal provided advice to the NHS on tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma [ID1441].
2. Before the appeal panel enquired into the detailed complaints the following made a preliminary statement:
	1. Jo Gumbs on behalf of OcuMel UK,
	2. Professor Mark Middleton on behalf of Melanoma Focus, who also read a statement on behalf of Professor Paul Nathan who was unable to attend the hearing to represent Melanoma Focus,
	3. Chris Hoyle and Mandy Turton on behalf of Immunocore; and
	4. Dr James Fotheringham on behalf of NICE.

## Appeal Ground 1a: In making the assessment that preceded the recommendation, NICE has failed to act fairly

### Immunocore appeal point 1a.2: NICE has failed to act fairly because the committee was required as a matter of procedural fairness to provide adequate explanations of their decision making as to their preferred modelling assumptions and failed to do so.

1. Chris Hoyle, for Immunocore, opened by reference to the appraisal committee's duty to adequately explain their decision with clarity pursuant to paragraph 6.1.9 of the NICE Guide to the methods of technology appraisal 2013 ("the Methods Guide").
2. He argued that no adequate explanation had been given in the final appraisal document (FAD) as to why the appraisal committee had preferred the evidence review group's (ERG) standard parametric modelling as opposed to Immunocore's own modelling. Further, in Immunocore's view, the committee failed to adequately explain the basis on which they considered standard parametric modelling to be less uncertain or more reliable than Immunocore’s modelling.
3. Chris Hoyle expressed his view that it was particularly important for the committee to provide compelling reasoning for preferring standard parametric modelling in the FAD because the approach was criticised by clinical experts in the second committee meeting. He also expressed his concern that no clinical input had been received by the ERG in preparing the model.
4. Dr James Fotheringham, for NICE, discussed that in the appraisal consultation document (ACD) the committee had explained why standard parametric modelling was generally preferred. He noted that tebentafusp had been evaluated across two appraisal committee meetings. In the first appraisal committee meeting, Immunocore had proposed a 'three-knot spline' model. In the ACD following the first committee meeting, the committee explained that while this fitted the observed data at the start of the curve, after a period of time the treatment arm of the model plateaued at a level above the observed data. That, combined with expert testimony in the meeting that ocular melanoma is very aggressive and real world evidence such as that from Rantala et al, led to the committee's interpretation that tebentafusp would not be curative, and meant that the committee were not in a position to accept the validity of that initial modelling method.
5. Dr James Fotheringham explained that the committee recommended in the ACD that standard parametric curves should be used as a starting point for modelling. By the second appraisal committee meeting Immunocore presented a flexible, piecewise model using a combination of both parametric and non-parametric modelling.
6. Dr James Fotheringham explained that the committee were not in a position to accept the piecewise model on the basis that Immunocore had failed to justify the data cut-points at which the curve moved from non-parametric to parametric modelling. Despite Immunocore having presented different models in both committee meetings, Dr Fotheringham concluded that neither model was sufficiently valid to persuade the committee that they were superior to standard parametric modelling.
7. In response, Chris Hoyle contested that the FAD incorrectly asserts that the parametric section of the model "generated extrapolations suggesting that people did not appear to die". Chris Hoyle was of the view that this and the committee's reference to 'curative', which is not claimed for tebentafusp demonstrated the committee's misunderstanding of the model and its failure to consider Immunocore's evidence on its choice of modelling in the second appraisal committee meeting.
8. Chris Hoyle argued that the ERG had made an incorrect assumption that parametric modelling is the standard approach to be used for immunotherapies. In doing so, the ERG had assumed similar shaped curves for both tebentafusp and pembrolizumab (the sole comparator requested by the appraisal committee between the first and second appraisal committee meetings). In deciding which model to use (and where to implement the hazard plots), Immunocore had considered both clinical evidence and historical data available. The clinical trial had also produced 18 months' additional data by the second appraisal committee meeting – which was provided and explained by Immunocore in an addendum.
9. The panel enquired whether, despite disagreeing with the committee's decision, Immunocore understood the reasons given by the committee in the FAD for preferring a different model.
10. Chris Hoyle replied that they did not. The committee's preference of the ERG model appeared to be based on a misunderstanding of what the committee interpreted as a curative effect implied by the Immunocore model, and their interpretation of that model from which they had concluded that no patients die. This misinterpretation discredits Immunocore's model – which left the committee with no option but to prefer the ERGs approach.
11. Aurelie Meunier, for Immunocore, said that the modelling assumptions used by the ERG were contrary to clinical expert advice heard in the appraisal committee meeting and that the committee had failed to adequately explain in the FAD why the ERG model was preferred when it departed from clinical input.
12. In response to a question from the panel, Dr James Fotheringham explained that the committee did not consider either of Immunocore’s survival models (presented in both committee meetings) as being valid options. For the first model, this was due to the perceived plateau effect towards the end of curve tail, and for the second model this was due to the change in hazards and small patient numbers.
13. Exploring the committee’s concern of small patient numbers in the piecewise model, the panel noted that small patient numbers are an inevitable consequence of appraising a treatment for any rare disease. Dr James Fotheringham answered by explaining that the piecewise model compounded the impact of a small trial population as there would have been an opportunity to utilise the entirety of the trial data by adopting standard parametric modelling from the beginning of the curve.
14. The panel turned to Dr Joe Sacco and Professor Mark Middleton (both for Melanoma Focus) for their clinical opinion of the use of the piecewise model in appraising tebentafusp.
15. Dr Joe Sacco expressed his view that it was entirely reasonable to adopt a piecewise model, since the curves depicted fitted biologically with immunotherapies. He compared the tail of the curve depicted in the tebentafusp arm of the piecewise model to a similar model adopted for appraising ipilimumab (another novel agent for a condition which did not have long term survival) both of which had smaller patient numbers towards the end of the curve. He added that clinicians were reticent to use the term “curative”, when in reality the best outcome expected was durable control.
16. Professor Mark Middleton agreed, noting that any suggestion other than a piecewise approach ought to be discounted.
17. Dr James Fotheringham noted that the committee was not explicitly presented with clinical input in their consideration of the different populations represented at different points in the survival curves.
18. Dr Steve Edwards, for NICE, explained that conceptually, in any mathematical modelling of survival, the preferred approach is usually the simplest approach possible if it meets the requirements of the data. For that reason, standard parametric modelling is usually the starting point. He further explained that a subset of parametric models could appropriately model an increasing hazard followed by a decreasing hazard, and that moving away from that approach would only be necessary if there was more than one change in hazards or if the curves produced were inadequate to reflect complexity. He explained that this parametric approach was the model adopted by the ERG. Further, he explained that where there are different populations or different make up of populations over time (as is suggested by Immunocore) – a piecewise model would not be the appropriate model to capture that.
19. Chris Hoyle agreed with Dr Steve Edwards that the starting point ought to be standard parametric modelling but argued that the suggested subset of parametric models required a larger patient population than was available in the clinical trial for tebentafusp, and so parametric modelling was inappropriate in this case.
20. Referring to paragraph 3.11 of the FAD, Chris Hoyle concluded that although the committee's uncertainty relating to Immunocore's model is captured – the FAD fails to provide any positive reason as to why the ERG's model was preferred.
21. The appeal panel concluded as follows. The panel noted that the committee had made clear in paragraph 3.11 of the FAD that their view was that standard parametric modelling of the overall survival in patients with advanced uveal melanoma, both for those receiving treatment with tebentafusp and with pembrolizumab, was their preferred option and should be the starting point. The panel noted that the reasons stated were largely as a result of the committee’s concerns with elements of the modelling of overall survival that was undertaken by Immunocore.
22. In this regard, the panel noted that the committee explained in 3.11 that there were concerns about the validity of the timing of the cut-point between the non-parametric and parametric elements of the piecewise survival curve generated by Immunocore in patients treated with tebentafusp; that there were small numbers of patients remaining at the point of the change in the hazards raising uncertainty about the generalisability of the results in a wider population; that the majority of the gains in survival that were used in the calculations of cost effectiveness were accrued in the extrapolated part of the curve; that the modelling led to an 'over-estimate' of the number of people surviving in the long-term; and that the curve resulted in a plateau in mortality that implied, in their opinion, that there was a curative effect of treatment that they considered implausible.
23. The panel noted, on the other hand, that it was explained in 3.11 of the FAD that the standard parametric modelling that was undertaken by the ERG did not lead to a plateau in mortality after the period of observed mortality and that the modelling resulted in a much lower long term survival than Immunocore's modelled curve.
24. While it was acknowledged in the FAD that clinical experts had indicated that, in view of the novel mechanism of action of tebentafusp, it was reasonable for the Immunocore to adopt different approaches to modelling long term survival in the two treatment arms of the study, the panel were satisfied, as a matter of fairness, that the committee had clearly explained the reasons for their preference for the use of standard parametric modelling in the 2 treatment arms that had been undertaken by the ERG.
25. The appeal panel concluded that the committee had acted fairly in providing sufficient explanation in the FAD of their decision-making as to their preferred modelling assumptions and dismissed the appeal on this point.

## Appeal Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE.

### Melanoma Focus appeal point 2.2: The committee’s statement (para 3.11) that “The committee considered that standard parametric curves should be the starting point for modelling and could be used for this treatment” is illogical and does not adequately reflect that non-parametric modelling has been established by NICE committees as the most appropriate (and now standard) methodology in immunotherapy appraisals. The committee and the ERG have failed to distinguish the most appropriate methodology for an immunotherapeutic despite precedent.

1. Professor Mark Middleton, for Melanoma Focus, opened by expressing his view that the committee had held the standard parametric modelling approach (used as its starting point) to a different evidential standard to the alternative piecewise model offered by Immunocore. Although concern was expressed by clinicians in the appraisal committee meetings about the use of parametric modelling, this was not explored further by the committee.
2. Dr James Fotheringham, for NICE, noted that the technology appraisal team had considered appraisals of similar immunotherapies, many of which had relied on parametric modelling. Both Dr Fotheringham and Dr Steve Edwards, for NICE, explained that it was incorrect to assume that one standard preference of modelling was entrenched in the appraisal committee's thinking. Instead, the committee considers which method is most appropriate in each case.
3. Chris Hoyle, for Immunocore, added that the choice of model should be informed by which best fits the observed data, informed both by mode of action of the drug and clinical input. He expressed the view that there had not been a systematic or balanced approach by the ERG to the selection of which was the most appropriate model and that very early on the committee disregarded the possibility of adopting a piecewise approach.
4. Aurelie Meunier, for Immunocore, explained that standard parametric modelling had been appropriate in the comparator arm of the model as pembrolizumab was not effective in this patient population. She noted that although there are some standard parametric models that could capture a change in hazards, the results would be clinically implausible for the tebentafusp arm.
5. Aurelie Meunier elaborated, explaining that where external long term-data is unavailable, clinical opinion should be relied upon. The clinical opinion heard in this case confirmed that there were a subgroup of patients who experienced long-term survival – something that could not be accurately reflected in a standard parametric curve. Consequently, Immunocore adopted a flexible model.
6. Dr Joe Sacco, for Melanoma Focus, concurred, explaining that pembrolizumab did not have immunotherapeutic effect in treating advanced uveal melanoma as it was not an effective treatment, unlike tebentafusp. He also noted that the evidence will inevitably be weaker where the cancer is rare and that it is necessary to rely on extrapolation to consider what lies beyond the horizon of the available data.
7. Mandy Turton, for Immunocore, added that tebentafusp has a wholly different mechanism of action to that of standard immunotherapies, and produces an extreme immunotherapeutic effect.
8. In response to a question from the panel, Dr James Fotheringham confirmed that the committee had not explicitly asked the clinical experts for their view on whether the model ought to be piecewise or standard parametric in the committee meeting. Instead, the committee heard evidence on the effects of tebentafusp on clinical outcomes and how these might relate to the survival modelling. The committee heard from the clinical experts that they were seeing individuals with a long-term treatment effect.
9. The panel referred to NICE’s Technical Support Document 21 (“TSD21”) which refers to clinical input in evaluating modelling plausibility. The panel enquired whether the committee heard expert input on the plausibility of one curve over the other. Dr James Fotheringham explained that the committee had heard evidence on the novel mechanism of action of tebentafusp and had applied that testimony to their expectation of the appropriate appearance of the curve.
10. Dr Jacoline Bouvy, for NICE, noted that there were clinical experts present at both committee meetings (which exceeds the standard practice of having clinical expertise in the first committee meeting only). Dr Joe Sacco explained that he had been put forward as an expert for the appraisal committee meeting, but that an ophthalmic surgeon (without experience of treating metastatic disease) had been selected instead. Dr Bouvy noted that the ERG was not represented in the appeal hearing, but agreed that their report does not refer to them having consulted clinical experts on this issue.
11. Professor Mark Middleton explained that a number of immunotherapies, despite having very different mechanisms of action, show a tail in the modelled survival curve. Although this would not be considered a cure, the immune response to treatment can be sustained in the long term by some patients. Given the effect of tebentafusp on T-cells, it is both mechanistically plausible and supported by patient data, for the treatment to result in long-term survival impact, as shown in the model.
12. The panel asked Immunocore how they had selected cut-points for the piecewise model, and whether this was explained to the committee. Aurelie Meunier discussed how the cut-points represent three different data sets, based on hazard changes, which was presented to the committee alongside the sensitivity analysis and the incremental cost effectiveness ratio's (ICERs) observed at each cut-point.
13. The appeal panel concluded as follows. The panel noted that in the IMCgp100-202 trial, in patients receiving tebentafusp, there was an initial increase and then a later decrease in the hazards. It was persuaded by the argument that was presented by the committee that standard parametric modelling can be legitimately applied when one inflection point in hazards is identified, as was the case in this study, and that complex modelling approaches are usually reserved for circumstances when there is more than one change in the observed hazards which was not the case in this instance.
14. The panel also noted the observation that five appraisals of immunotherapy treatments have been undertaken by NICE in the last 12 months in which parametric approaches to modelling have been undertaken but also accepted that appraisals have been undertaken in which non-parametric modelling approaches have been used. On balance, the panel was not convinced that a precedent for the preferential use of non-parametric modelling has been established in NICE appraisals of immunotherapy treatments, nor that their use is now regarded by NICE as standard. Rather, it was persuaded that the preferred modelling approach is tailored to the available data in each NICE appraisal.
15. The appeal panel therefore dismissed the appeal on this point.

### Immunocore appeal point 2.3: The committee's conclusion that overall survival modelling is highly uncertain and standard parametric approaches are the most appropriate to apply to both treatment arms, cannot reasonably be justified.

1. Aurelie Meunier, for Immunocore, explained that Immunocore had taken steps to minimise the uncertainty in survival modelling by using both historic data and clinical opinion to support the survival modelling employed. She expressed Immunocore's view that the committee had disregarded the clinical input supporting the modelling, tebentafusp's unique mechanism of action and precedents for modelling survival in immunotherapies. Further, Immunocore's approach was supported by TSD21.
2. Aurelie Meunier argued that the committee's reliance on ERG modelling was unsound and unreasonable as it over-estimated survival, and produced convergence and then crossing of the survival curves of the comparator and treatment arms, showing higher long-term survival with the comparator than with tebentafusp. This was at odds with tebentafusp's known effect of reducing death in approximately 50% of patients.
3. Dr James Fotheringham, for NICE, explained that the committee had been presented with uncertain modelling by both Immunocore and the ERG. This was noted in the ACD, and is exemplified by the range of ICERs presented under the different modelling approaches.
4. Dr Steve Edwards, for NICE, distinguished between the uncertainty resulting from the paucity of evidence arising from rarity of the disease, and the uncertainty caused by the immaturity of trial data. In this case, he was of the view that there were sufficient patients involved in the trial, and so rarity of the disease had not caused uncertainty. Rather, the uncertainty was related to the immaturity of the data; i.e. patients have not been in the trial long enough to produce survival data that enabled a relatively certain 'tail' for the model. He further explained his view that the change in hazards could be captured adequately by using standard parametric modelling, which could cope with a single inflection point in the hazard plot. The cut-points selected by Immunocore had influenced the final ICER as Immunocore had adopted a non-standard approach to the parametric curve after the cut point. Dr Steve Edwards explained that the standard approach would be to use all the Kaplan-Meier survival data before the cut-point to predict the tail of the curve, but Immunocore had used the Kaplan-Meier data just before the cut point to estimate the later survival. In his view, the selection that Immunocore made over emphasised the survival for tebentafusp, and underestimated the survival for the comparator, and he could not see an adequate basis for accepting those apparently arbitrary approaches.
5. As a result, said Dr Steve Edwards, the committee was presented with a scenario by the ERG that was considered to have a level of plausibility, whereas Immunocore’s choice was considered to have issues that were not resolved and that were not resolvable through discussion. He appreciated that the ‘truth’ might fall between the two models, but highlighted that the committee was not presented with any alternative models.
6. Aurelie Meunier disagreed with Dr Steve Edwards’ interpretation of the standard approach to incorporating Kaplan-Meier data, and his view that this resulted in an underestimate of survival in the comparator arm. She explained that pembrolizumab is not an effective treatment for advanced uveal melanoma (as supported by the historical data presented by Immunocore). She further questioned how the appraisal committee had concluded that the ERG’s model was more plausible given their failure to consult with clinicians. Dr Joe Sacco, for Melanoma Focus, concurred, noting that the standard parametric approaches do not capture what is biologically plausible.
7. The panel questioned why the committee had chosen to disregard Immunocore's approach given that the approach was informed by TSD21. Janet Robertson, for NICE, explained that although TSD21 explains the options available if a more complex model is adopted, it does not necessarily say that a complex model should be adopted. Dr Jacoline Bouvy, for NICE, concurred, noting that the TSD21 sets out best practice for cases with complex hazard functions that require a move beyond standard parametric techniques. In this case, she explained that the committee were not persuaded that standard techniques were not appropriate.
8. The panel enquired why the committee considered the ERG’s model to be more plausible given that it had not been informed by clinical expertise, and that its validity had been challenged by clinicians in the second appraisal committee meeting.
9. Both Dr James Fotheringham and Dr Steve Edwards explained that it had been a challenging decision to make. Dr Fotheringham summarised the position by saying that there was not sufficient evidence that more complicated survival modelling was required in this situation, notwithstanding the fact that the ERG model had not been informed by clinical advice.
10. Chris Hoyle, for Immunocore, re-iterated that no positive reasons for preferring the ERG’s model had been advanced by the committee in their reasoning. Chris Hoyle acknowledged that Kaplan-Meier estimates can overfit the data – but that this was accommodated by Immunocore as they had verified its validity with clinical input.
11. The panel questioned whether the clinicians were explicitly asked about the clinical plausibility of the comparator arm at the committee meeting. Neither Dr James Fotheringham nor Dr Steve Edwards could recall this being considered, and confirmed that that no explicit reference was made to this in the FAD.
12. Dr Steve Edwards explained that the committee was concerned by Immunocore's use of different survival functions in each arm. Technical Support Document 14 ("TSD14") requires strong rationale to adopt differing functions in survival modelling. The committee, based on the raw data provided, were not persuaded that such an approach was justified in this instance. The panel responded noting that TSD14 also provides that piecewise models are useful tools where differing hazards are observed.
13. Dr James Fotheringham noted that neither the model presented by the ERG nor Immunocore gave rise to a plausible ICER. The panel questioned whether access to the cancer drug fund had been considered, Dr Fotheringham explained that this was not an option available to the committee in this instance as the ICER presented would not permit entry into the cancer drug fund.
14. The appeal panel concluded as follows. In considering this point, the panel noted that there was general agreement that tebentafusp is a new agent with a novel mode of action and that the IMCgp100-202 trial is a landmark study aimed at defining its benefits in patients with advanced uveal melanoma. No other data is currently available to establish the impact of tebentafusp on long term survival in this clinical context, and the availability of long-term follow-up data from the study is not yet forthcoming. The panel was persuaded that the use of modelling approaches to estimating long term survival are necessary but inevitably involve an element of uncertainty, particularly in regard to accurately predicting the nature of the tails of the survival curves in the presence of relatively immature data. Nonetheless, it concluded that the preferred approach adopted could have been better informed by the input of clinical experts with expertise in the use of immunotherapy treatments in this clinical context, particularly when high levels of uncertainty exist. In coming to this conclusion, the panel also noted that in circumstances such as these NICE Decision Support Unit Technical Support Document 21 advises that consideration should be given to whether the extrapolation is realistic, which may involve using external data sources, clinical expert opinion, or arguments around biological plausibility*.*
15. The panel accepted the argument presented by the committee that the hazard functions and survival with tebentafusp that were observed in the IMCgp100-202 trial did not mandate a complex approach to the modelling of long-term survival, but it also noted that the committee had concluded that the approach adopted by the ERG was far from perfect. The panel were persuaded that, from a methodological point of view, it was not unreasonable for the committee to state a preference for the use of standard parametric modelling in the two treatment arms that was presented by the ERG. On the other hand, and faced with significant degrees of uncertainty, it would have expected the committee to ensure that there had been input of clinical experts with experience in the management of advanced uveal melanoma and with an understanding of the potential impact on the disease of a novel immunotherapy treatment to advise the work of the ERG and to support the committee's decision-making process in this regard.
16. The panel were not presented with any evidence that the ERG had considered the input of clinical experts in arriving at its decisions about the optimal approach to the modelling of long-term survival in this appraisal. Furthermore, while experts with acknowledged experience of managing advanced uveal melanoma were recruited by Immunocore to advise their modelling approaches and to attend the two committee meetings, it appears that the criticisms that they presented about the modelling approach adopted by the ERG were disregarded by the committee and were not countered by any alternative expert opinion. The panel concluded, therefore, that faced with two different approaches to the modelling of survival with tebentafusp treatment, neither of which the committee considered to be ideal, the committee had acted unreasonably in not ensuring adequate input from clinical experts in helping them resolve areas of important residual uncertainty.
17. The appeal panel therefore upheld the appeal on this point.

**Immunocore appeal point 2.2: The Committee's decision to apply standard parametric modelling to overall survival cannot reasonably be justified because it led to clinically implausible results, namely in the EAG's model, the estimate of 5 year survival in the comparator arm is 4-fold higher than published historical data.**

1. Aurelie Meunier, for Immunocore, said that clinical experts expressed their concern in the second appraisal committee meeting that the ERG extrapolation demonstrated a 5 year survival of circa 12% in the comparator arm. This survival rate would be 4-fold higher than the published historical data.
2. Dr James Fotheringham, for NICE, explained that the committee had considered the information generated in the present clinical trial as being the best data in assessing the efficacy of pembrolizumab. The committee considered that it was unreasonable to rely on the historical data presented, where that data spanned a period of 37 years in which only 2-4% of participants received pembrolizumab.
3. The panel asked whether the committee had heard clinical evidence in the committee hearings which would inform its assessment of the comparator values. The committee did not recall explicit reference to this issue in the meetings.
4. Chris Hoyle, for Immunocore, noted that the issue had been identified by both Immunocore and Professor Nathan (one of the clinical experts) in the second appraisal committee meeting.
5. Dr Steve Edwards, for NICE, explained that it was not unusual to see survival projections in clinical trials being higher than what is expected in clinical practice, and that an element of judgment is needed to evaluate how informative the tail of a Kaplan-Meier estimated curve is. He explained that because of the nature of the randomisation and the relatively few patients randomised to the comparator arm compared to tebentafusp, the trial produces a tail for the comparator arm that is of limited value. Dr Joe Sacco, for Melanoma Focus, noted that the curve presented in the ERG model does not fit with any trial data nor clinical input.
6. The appeal panel concluded as follows. The panel accepted the arguments proposed by the committee that the published historical data is of limited value in helping to resolve this issue and to provide reliable validation. It noted that the most relevant study, Rantala et al. 2019, had included very few patients receiving pembrolizumab and it was also aware that the majority of those patients treated with checkpoint inhibitor immunotherapy agents (such as pembrolizumab) that were included in this study, were doing so as second line treatment. The panel were persuaded that the published historical data was not able to satisfactorily resolve the issue of the plausibility of the ERG modelled 5-year survival data following treatment with pembrolizumab in advanced uveal melanoma.
7. The appeal panel, once again, noted the uncertainties in the minds of the committee about the legitimacy of the different modelling approaches of overall survival which were presented by the ERG and Immunocore. Under these circumstances, the panel were persuaded that the availability of external data or expert opinions would be of particular importance in validating one approach or another to the modelling process and to help resolve uncertainties. Specifically, the panel concluded that the need for the committee to determine the plausibility of the extrapolated 5-year survival in the comparator arm of the ERG model is of particular relevance to understanding the reasonableness of the approach they supported.
8. The panel agreed with the committee that there was considerable uncertainty in the interpretation of the Rantala data, and in that context the panel considered that the input of clinical experts was of potentially greater importance to the committee in understanding the most plausible estimates of 5-year survival with pembrolizumab. It noted that concerns had been expressed by an expert attending the second committee about the plausibility of the 5-year survival estimates that resulted from the ERG modelling in the comparator (pembrolizumab) arm. It also noted the expert opinions that were expressed in the hearing that pembrolizumab is ineffective for the treatment of advanced uveal melanoma and that an 11.6% 5-year survival is implausible. The panel accepted the observation by the committee that there was a plateau in survival noted in the pembrolizumab arm of the study but also noted their submission that this may be misleading and be explained by the relatively small number of patients that remained in the comparator arm.
9. The panel concluded that the NICE committee had acted unreasonably in not adequately considering the opinions of clinical experts in understanding the plausibility of the 5-year survival that was estimated by the modelling approach adopted by the ERG in the comparator arm and preferred by the committee.
10. The appeal panel therefore upheld the appeal on this point.

**Immunocore appeal point 2.5 and Melanoma Focus appeal point 2.1:**

1. These two appeal points both related to the reasonableness of the committee’s conclusion that Immunocore’s modelling of overall survival with tebentafusp over-estimated long-term survival and that tebentafusp was curative in some patients with advanced uveal melanoma. Although they were taken sequentially in the hearing, they were therefore considered together in the panel’s deliberations and the panel’s conclusions are therefore presented in this decision letter as such.

**Immunocore appeal point 2.5:** **The committee's conclusion that the Company's modelling overestimated the proportion of people surviving in the long term, because it generated extrapolations suggesting that people did not appear to die in the period modelled by the parametric section is incorrect. This demonstrates that the committee misunderstood the modelled survival data, and therefore the committee's conclusion cannot reasonably be justified.**

1. Aurelie Meunier, for Immunocore, stated that the committee had fundamentally misunderstood Immunocore's model. She explained that the mean age of diagnosis is 62 and the model adopts an age adjusted mortality of 75. Up to the age of 75, patients are modelled as dying at a higher rate than background mortality (i.e. the mortality rate for the general population of that age). Over that age, the age adjusted mortality rate (i.e. background mortality) is applied. Mandy Turton, for Immunocore, further argued that it was incorrect for the committee to conclude that Immunocore's modelling overestimated long term survival. The elongation of the survival curve against background mortality is entirely plausible and represents the long term survival benefit experienced by a discrete group of patients taking tebentafusp. A small group of patients can achieve long term disease control, but this does not amount to a cure. The committee had misunderstood the implication of survival modelling beyond the time period of the trial.
2. Dr James Fotheringham, for NICE, noted that from year 13 onwards in the modelling, the patients taking tebentafusp had the same death rate as the general population, which implies they are "cured". Dr Steve Edwards, for NICE, agreed, and noted that in the modelling – there is a "structural cure".
3. Chris Hoyle, for Immunocore, explained that patients who are successfully treated with immunotherapies are able to live with the disease, as is shown in the model. That does not equate to a curative effect. Dr Steve Edwards disagreed, noting that although Chris Hoyle's view is one interpretation of the model, in his view the long term extrapolation of the model is an overestimate of what the committee expected to see, meaning that mortality had to be capped at the rate of background mortality, because there is no plausible explanation as to why the mortality rate for tebentafusp would be better than the background mortality rate.
4. The panel enquired why the committee concluded that it was unreasonable to adopt different approaches in both arms of the model given the marked difference in hazard plots.
5. Dr James Fotheringham explained that there was uncertainty about the nature of changes in hazard over time due to the small number of patients. Dr Steve Edwards elaborated, noting that although it may be reasonable to use different survival models to fit both treatment arms, there are standard parametric models that can accommodate a change in hazards.
6. The panel questioned why, if it was considered reasonable to use different survival models in each treatment arm, the committee did not prefer Immunocore's modelling. Dr James Fotheringham replied that there was insufficient evidence to recommend Immunocore's survival modelling over the ERG's model.
7. In response to a question from the panel, Dr James Fotheringham explained that the committee's conclusion that Immunocore’s model overestimated survival in the active treatment arm carried greater weight in the committee's reasoning, than the conclusion that the model suggested 'people did not appear to die'.
8. The panel enquired about the extent to which the committee had taken into account the impact of disease rarity on the certainty of modelling. Dr James Fotheringham explained that the committee were unable to consider rarity as there was no plausible ICER presented. As a result, the discussion did not reach the stage at which rarity would be considered.
9. Dr Jacoline Bouvy, for NICE, oted that the uncertainty at the tail of the curve related to lack of long term follow up data rather than the small number of patients owing to rarity.
10. Chris Hoyle disagreed, and referred to the committee's decision at paragraph 3.11 of the FAD which links their view of overestimated survival with the erroneous assertion that Immunocore's model generated extrapolations suggesting that people did not appear to die in the period modelled by the parametric section.

**Melanoma Focus appeal point 2.2: The committee's statement at paragraph 3.11 of the FDG that the "clinical experts suggested that uveal melanoma is an aggressive disease and that there is no expectation that tebentafusp would be curative. So it is not expected that the overall survival curve would plateau" is flawed, misinterprets expert opinion and makes an inappropriate conclusion to justify use of parametric curves.**

1. Professor Mark Middleton, for Melanoma Focus, explained that as uveal melanoma is an aggressive disease, there is no expectation of tebentafusp being curative. Nonetheless, some patients being treated with tebentafusp have experienced long term disease control.
2. Dr James Fotheringham, for NICE, expressed the committee's view that in terms of epidemiological survival risk, long term control allowing a patient to live with the disease and having the same survival as the background population is regarded as the same as being cured.
3. Dr Joe Sacco, for Melanoma Focus, explained that clinicians consider it plausible for the model to display a long term survival plateau where patients have a similar mortality to the background population. The committee, on the other hand, concluded that as this was an aggressive disease, a curative effect was not expected and that therefore this demonstrated that Immunocore's modelling was incorrect.
4. Dr Steve Edwards, for NICE, said that there is evidence which shows long-term disease control with pembrolizumab in other diseases which produces a plateau in the survival curve. For tebentafusp, on the other hand, although this might be plausible, this has not yet been proven.
5. On Immunocore's appeal ground 2.5 and Melanoma Focus' appeal ground 2.1, the appeal panel concluded as follows.
6. The panel noted the evidence presented by Immunocore that they had applied age-adjusted mortality to their modelling that meant that there was a higher than background mortality for the first 13 years, but mortality rates were equivalent to the age-adjusted population thereafter. It noted Immunocore's explanation that this meant that patients would continue to die throughout the follow-up period but that tebentafusp has the potential to deliver long-term disease control in a sub-group of patients.
7. The panel noted that the committee were aware that Immunocore had applied age-adjusted mortality to their modelling and that this, in itself, had raised some concerns in the minds of the committee about the validity of the modelling approach adopted by Immunocore since they considered there to be no plausible explanation as to why mortality following treatment with tebentafusp might be lower than in the general population. The panel also noted that the conclusion that the committee had reached, that Immunocore modelling implied that tebentafusp was 'curative' in some patients in the long term, was based on the observation that after 13 years, the modelled survival curve showed that patients treated with tebentafusp that were still alive were assumed to have a mortality equivalent to that of the background population. It noted, also, that the committee acknowledged that this was a 'structural cure' that resulted from the modelling undertaken by Immunocore rather than from trial observations.
8. The panel noted the opinions that were expressed by clinical experts that long-term disease control following treatment with a novel immunotherapy agent such as tebentafusp, in the context of an advanced and aggressive disease such as uveal melanoma, is neither unprecedented nor implausible. It was also persuaded that Immunocore had not made any claims about the possibility of tebentafusp providing a cure for this disease or that there was any implication that patients would not continue to die in the long term after treatment with tebentafusp despite the plateau in the modelled survival curve. The panel considered that the input of experts is essential before conclusions can be legitimately drawn about the extent to which modelled estimates of long-term survival are regarded as appropriate and plausible or not. The panel were not informed of any attempts made either by the ERG or the committee to recruit or consider additional expert advice in considering the plausibility of the extrapolated survival curves resulting from Immunocore's modelling and concluded that the committee had acted unreasonably in this regard.
9. The appeal panel therefore upheld the appeal on both these points.

**Immunocore appeal point 2.7: the committee's decision to apply standard parametric modelling to overall survival is unreasonable because it does not reasonably take into consideration the fact that advanced uveal melanoma is an ultra-rare disease with only 100 patients per year expected to be eligible for tebentafusp, and does not recognise the vulnerability of the very small patient group facing terminal disease without other proven treatment options.**

1. Chris Hoyle, for Immunocore, explained that the committee had not cited the prevalence of advanced uveal melanoma in the FAD. By adopting the standard parametric modelling used by the ERG, the committee had failed to consider the lack of other treatment options available to this small patient group. He argued that a rationale based on uncertainty was unreasonable when the patient population was unavoidably small. He argued that an allowance should have been made for that.
2. Dr James Fotheringham, for NICE, concurred with the statement that this appraisal considered a vulnerable patient group facing an aggressive disease. He appreciated that Immunocore had, despite the rarity of the disease, performed a moderately sized clinical trial, representing the best evidence available.
3. Dr James Fotheringham noted that the committee was not presented with a plausible cost-effective ICER in this case (following the application of confidential discounts). Nevertheless he explained that in situations where the committee is presented with a range of ICERs, one of which might be cost-effective, then the consideration of decision risk would inform whether or not the committee felt able to recommend the drug based on an ICER informed by more conservative extrapolations for rarer disease. He confirmed, however, that in the absence of a plausible cost-effective ICER, that was not relevant in the current appraisal.
4. The panel asked how (if at all) rarity was taken into consideration by the committee. Dr James Fotheringham explained that the committee did not need to consider rarity because the evidence base presented by Immunocore was strong given the small patient numbers. Dr Steve Edwards, for NICE, agreed, and described how rarity is usually taken into consideration in instances where the patient population is so small that companies are required to run single arm trials with very small patient groups. This is in stark contrast to Immunocore's clinical trial for tebentafusp which was a moderately sized randomised control trial.
5. Dr Joe Sacco, for Melanoma Focus, argued that it was unreasonable for the committee to discount rarity as a result of Immunocore's efforts to develop a strong trial. Immunocore's intention in conducting the trial was to build a strong body of evidence to support the NICE appraisal. Instead, the committee had discounted the rarity of the disease as a result of the strength of evidence from Immunocore's trial. He explained that due to the aggressive nature of the disease and small patient population, the evidence presented by Immunocore is the best evidence that will be available for uveal melanoma.
6. Dr James Fotheringham explained that the committee's concern arose from the decreasing number of patients remaining in the trial towards the end of the survival curve, and not the small number of patients overall owing to rarity of disease. This was an issue with the maturity of the trial data, not rarity *per se*.
7. The appeal panel concluded as follows. The panel were satisfied that the committee had recognised that advanced uveal melanoma is an aggressive disease in which there is an unmet need in regard to effective treatment options available and a poor clinical prognosis. The panel were also persuaded that the committee had acknowledged the considerable achievements of Immunocore in undertaking a high quality randomised controlled trial (RCT) that included a ‘moderate’ number of patients despite the relative rareness of this disease. The panel accepted the explanation that was provided by the committee that the relatively small numbers of patients that remained in follow-up in the IMCgp100-202 trial is most likely to be because of the aggressive nature of the underlying disease process, rather than the non-availability of trial participants as a consequence of rarity, and that the maturity of the trial data will improve with the passage of time.
8. The panel noted that the committee do, under certain circumstances, make allowances for the rarity of a disease and the vulnerability of the patient population in its decision-making processes. It understood that this is particularly the case when they are presented with a range of ICERs, one of which might be cost effective, and the rarity of the disease may then influence their approach to decision risk and the possible acceptance of a cost effective ICER informed by more conservative extrapolations. The panel noted that the committee considered that this was not the case in this appraisal since they explained that they had not been presented with a cost effective ICER following the application of confidential discounts.
9. The panel were persuaded that the committee were faced with limited opportunity to incorporate the important considerations of the rarity of advanced uveal melanoma, the absence of effective treatment options other than tebentafusp and the poor clinical prognosis into their decision-making process in the absence of a cost effective ICER. It concluded that the panel had acted reasonably in these regards.
10. The appeal panel therefore dismissed the appeal on this point.

**OcuMel UK appeal ground 2.1: The committee’s decision to adopt modelling using monthly best supportive care costs is unreasonable because the ERG and/or the Committee did not take due account of appropriate experts in reaching their views.**

**Immunocore appeal ground 2.6: The committee’s apparent endorsement of a monthly best supportive care costs model was unreasonable in the light of clinical experts’ comments in support of a one-off aggregated cost model.**

1. These two appeal points both related to whether the committee had reasonably considered the opinions of experts when stating the preference for the use of monthly supportive care costs, rather than a “one off” model, and were therefore considered together (with the agreement of all present) during the hearing and in the panel’s deliberations. This decision letter therefore considers both together.
2. Jo Gumbs, for OcuMel UK, set out OcuMel UK's view that the experience of patients engaged with OcuMel UK and living with advanced uveal melanoma are at odds with the concept of monthly supportive care costs being applied in appraising tebentafusp.
3. Victoria McMorran, for OcuMel UK, talked in her capacity as a melanoma clinical nurse specialist. She explained that in her experience, patients with uveal melanoma (even when metastatic) can remain well for a long period of time before very rapid deterioration. Until very near the end of life, the supportive care needs of those receiving tebentafusp are small, and are thus different to the support needs of those with other types of metastatic cancer.
4. Mandy Turton, for Immunocore, also described how the inclusion of monthly best supportive care costs does not reflect the fact that most patients with uveal melanoma do not require supportive care until the last few months of life. She argued that this point was explained by clinical experts, but disregarded by the EAG and the committee. She argued that the committee's conclusion, expressed in paragraph 3.15 of the FAD was consequently unreasonable.
5. Dr James Fotheringham, for NICE, explained that the evidence informing the monthly best supportive care costs was taken from a multiple clinical expert elicitation exercise, published across a range of geographies and including a Delphi consultation process. That evidence was elicited on a monthly basis and the clinicians responding to the consultation were therefore asked for 'the monthly cost'.
6. Dr James Fotheringham said that the ERG had applied one off costs at three points in the model – at the beginning of treatment, at progressed disease state and at a time prior to death. The committee sought expert opinion from the clinicians present on this specific point, to understand the duration of best supportive care needs.
7. Dr James Fotheringham explained that in any case, the costs did not have a large impact on the ICER (circa £500) and so were highly unlikely to influence the committee's recommendation. Chris Hoyle, for Immunocore, disagreed with this, stating that the ICER was increased by £15,000 due to the best supportive care costs being applied.
8. Both Professor Mark Middleton, for OcuMel UK / Melanoma Focus and Dr Joe Sacco, for Melanoma Focus, confirmed that since the most common metastases of uveal melanoma were hepatic, the best supportive care costs would remain low until very near to end of life.
9. Aurelie Meunier, for Immunocore, described how Immunocore had modelled the quality of life variance using EQ-5D data which replicated patient experience as accurately as possible. As with many other melanomas, the patient can lead a normal life until a few months before end of life. This can usually be modelled using a "time to death" approach. However, this was not possible in the clinical trial for tebentafusp due to the small trial population. Instead, Immunocore had analysed the data based on treatment status (i.e. receiving and not receiving treatment for uveal melanoma), and applied multipliers derived from the pembrolizumab appraisal.
10. Chris Hoyle and Dr James Fotheringham both confirmed that the utility values only start to decline around a year before death – with the utility values at the beginning of the study being 0.8, and the utility value 90 days before death being 0.3.
11. Christian Griffiths, for NICE, noted that the functionality which would inform the best case was not available to the ERG despite having asked Immunocore for it.
12. The appeal panel concluded as follows. The panel noted the compelling testimonies that were presented by patient experts during the hearing in which they described their experiences of either living with uveal melanoma themselves or observing the impact of advanced disease on a family member. The panel also took note of the experiences of clinical experts who described how patients may lead full and active lives, despite the presence of advanced disease progression, and be spared significant symptoms until relatively soon before death. The panel understood the explanation that was provided by experts that this is because the presence of advanced metastatic disease in the liver may not necessarily be associated with symptoms in view of the relatively 'forgiving' nature of this organ.
13. The panel accepted that published evidence is available (McKendrick *et al.* 2016) which captures the monthly supportive costs associated with the care of patients with metastatic skin melanoma but also noted that this study had formed the basis of Immunocore's conclusion that the aggregation of best supportive care costs for 4 months was the most appropriate to apply to the model in view of the observed natural history of advanced skin and uveal melanoma. The panel also noted that the data from this study had been modified through the input of 2 UK clinical experts, to ensure that the costs were specifically appropriate for patients with uveal melanoma.
14. The panel were persuaded that the input of clinical and patient experts is essential to adequately understand the best approach to applying best supportive care costs in the model, in view of the described unusual clinical course of advanced uveal melanoma. The panel noted that there was no evidence presented that the ERG had sought expert input in determining their preferred approach to the application of best supportive care costs and the panel were not convinced that the committee had made sufficient effort to consider additional expert advice before arriving at their own conclusions. The panel considered that the committee had acted unreasonably in this regard.
15. The appeal panel therefore upheld the appeal on both these points.

##  Conclusion and effect of the appeal panel’s decision

1. The appeal panel therefore upholds the appeal on the following grounds: Immunocore 2.2; Immunocore 2.3; Immunocore 2.5; Immunocore 2.6; Melanoma Focus 2.1; Ocumel UK 2.1.
2. The appraisal is remitted to the appraisal committee who must now take all reasonable steps to correct the issues identified above. Specifically, it is the panel's view that reasonableness requires they should seek additional expert clinical input on areas of important residual uncertainty, notably the most appropriate choice, and interpretation of survival curve models to interrogate the available data, and the most appropriate means of allocating supportive care costs in the model. Immunocore should be given the opportunity to comment on this expert advice. These reconsiderations could lead to further review of the cost effectiveness of tebentafusp for the treatment of advanced uveal melanoma.
3. The appeal panel dismissed the appeal against this appraisal on all other grounds.
4. There is no possibility of further appeal against this decision of the appeal panel. However, this decision and NICE’s decision to issue the final guidance may be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made within three months of NICE publishing the final guidance.