NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

# Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma [ID1441]

# Committee Papers

NICE National Institute for Health and Care Excellence

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

# Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma [ID1441]

**Contents:**

The following documents are made available to consultees and commentators:



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

# Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma

## Single Technology Appraisal

## Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

**Type of stakeholder:**

**Consultees –** Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

**Clinical and patient experts and NHS commissioning experts** – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

**Commentators –** Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

**Public –** Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

**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 number | Type of stakeholder | Organisation name | Stakeholder comment<br>Please insert each new comment in a new row | NICE Response<br>Please respond to each comment |
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| 1 | Patient expert | | I agree with the submission made by OcuMel Uk by [redacted]<br>I particularly agree with the comments made in section 1, I am pleased to see that the committee has taken on board the severity of metastatic uveal melanoma and the effects on mental health of patients having uveal melanoma. I still do not think the committee have taken on board the fact that there is not one effective treatment available on the NHS to patients who go on to develop metastatic uveal melanoma. This is a huge worry and really must be taken into consideration. | Comment noted. Thank you.. The committee carefully considered the evidence and considered the views of clinical experts and patient/carer representatives when forming its recommendations Please see section 3.1 and 3.2 of the FAD |
| 2 | Patient expert | | 3.4 I am pleased to see that Tebentafusp has been recommended as first line treatment for metastatic uveal melanoma and can be used as second line treatment if required. | Comment noted. |
| 3 | Patient expert | | 3.10 Overall survival with tebentafusp<br>I think the committee has over stressed some of the uncertainty around modelling for overall survival and hopefully when Immunocore submit data in the preferred mode the committee can look at it more favourably. I feel like the whole overall effect of overstating any uncertainty has been to diminish the benefit that tebentafusp has most certainly offered to patients. This is a novel drug and patients I have spoken have most certainly benefitted from treatment. NICE want to see longer follow up of patients up to five years from start of treatment. This statement is exceptional if you look at the survival rates of untreated patients with metastatic uveal melanoma. It is a very aggressive disease and patients may only last a few months, or maybe up to 12 to 14 months if they are lucky. The prospect of living beyond two years, maybe up to five years would be a fantastic prospect for any stage four patient! I do not think the committee has grasped the very short time that some patients can survive without treatment. | Comment noted. Thank you. The committee further considered the modelling of overall survival at the second committee meeting. Please see section 3.11 of the FAD for its conclusions. |
| 4 | Patient expert | | 3.12 I am very pleased to see that the committee have concluded that it is not appropriate to stop treatment with tebentafusp after two years in patients who are responding well. | Comment noted. |
| 5 | Patient expert | | 3.14 Testing for HLA-A*02:01 Feedback from patients I have spoken to have said that this testing can take up to six weeks to get the results back thus delaying the start of treatment. Would it be possible to improve this delay at all? | Comment noted. The committee makes its recommendations, in line with the remit for the topic being considered. Implementation and time taken for HLA-A*02:01 testing was not part of the remit for this Technology Appraisal. |
| 6 | Patient expert | | 3.19 Tebentafusp has not been recommended for inclusion in the Cancer Drugs Fund This is very disappointing. At what point will this be reviewed? The MHRA has approved tebentafusp for safety and efficacy but now the drug will only be available to | Comment noted. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's |

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| | | | those patients with sufficient health insurance or sufficient funds to self-fund treatment. This means that the only drug approved for use will be inaccessible to all but a very few patients. | Cancer Drugs Fund methods guide (addendum).The committee concluded that tebentafusp could not be recommended for use in the Cancer Drugs Fund (see section 3.23 of the FAD). |
| 7 | Patient expert | | Are the provisional recommendations sound and a suitable basis for guidance to the NHS?<br>No, I do not agree that the recommendation not to approve tebentafusp either for use on the NHS or the Cancer Drugs Fund is sound. The burden of illness to patients, the aggressive nature of the cancer and short life expectancy once diagnosed as stage 4 and the constant scanning of patients to check for metastatic growth has not been adequately considered in relation to the full benefits that this new drug can offer. There is more data to come, but in the mean time there is a clear benefit from treatment. | Comment noted. The committee considered further clinical evidence and the views of clinical experts and patient/carer representatives were further considered by the committee during the second committee meeting and when formulating its recommendations. The committee discussed the potential for inclusion in the Cancer Drugs Fund, but the cost effectiveness estimates presented did not show plausible potential for tebentafusp to be cost effective. See 3.23 of the FAD. |
| 8 | Consultee | OcuMel UK | **Has all the relevant evidence been taken into account?**<br>Unmet need<br>We welcome the recognition of the severity of metastatic uveal melanoma and the acknowledgement that there is a burden on all uveal melanoma patients from regular scans and anxiety about developing metastases. This patient community are aware there are very limited treatment options.<br><br>Tebentafusp is a novel therapy and the first treatment that has shown a survival benefit for metastatic Uveal Melanoma patients. We are concerned that the recommendation does not fully recognise the unmet need of metastatic uveal melanoma patients who have no other treatment options.<br><br>Wider benefit<br>The wider benefit of Tebentafusp has also not been adequately considered. 50% of uveal melanoma patients will develop mets which have very few treatment options and a very poor prognosis.<br><br>All patients with uveal melanoma live with the prospect of developing metastatic disease.<br><br>All patients live with the anxiety of “watching and waiting” with regular testing for metastatic disease.<br><br>The extent to which these impact on patients’ Health Related Quality of Life and the real benefit of an effective treatment to even those patients who have not (yet) developed metastatic disease, has not been fully taken into account. | Comment noted. The committee carefully considered the unmet need in section 3.1 and 3.2 but concluded that there were no additional benefits which had not been captured in the QALY calculations (see section 3.17 of the FAD for the committee discussion). |
| 9 | Consultee | OcuMel UK | **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** | Comments noted. The committee considered the clinical and cost effectiveness evidence further at the second committee meeting and carefully considered |

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| | | | We note the committee's concern with the modelling for overall survival and hope that Immunocore will submit data using the preferred approach which addresses the committee's concerns and improve the overall clinical and cost effectiveness of Tebentafusp.<br><br>However, uncertainty about overall survival is common for new oncology treatments and we would consider that any clinical uncertainty could form the basis of a referral to the CDF rather than resulting in patients having no treatment options.<br><br>We do not consider the committee to have made reasonable interpretations of the evidence in regard to unmet need and the wider benefit of Tebentafusp (see earlier comments). | this when making its recommendations. |
| 10 | Consultee | OcuMel UK | **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**<br>Given our comments above, we do not agree that the recommendations are sound as they do not adequately reflect the burden of illness and the full benefits of Tebentafusp. We agree that a two-year stopping rule would lack a clear clinical rationale and would not be appropriate to include in guidance to the NHS. Treatment should be made available to patients who are continuing to benefit from it beyond an arbitrary 2 year cut off. | Comment noted. The committee considered further clinical evidence and the views of clinical experts and patient/carer representatives were further considered by the committee during the second committee meeting. The committee concluded that it was not appropriate to include a stopping rule in the model (see section 3.13 of the FAD). |
| 11 | Company | Immunocore Ltd. | *Page 3 – ''Tebentafusp will be higher than an acceptable use of NHS resources''*<br><br>*The NHS England Budget Impact Assessment (BIA) showed that due to the small number of patients, tebentafusp would be under the budget impact threshold set by the NHS. The Budget Impact Assessment by NHSE stated that ''given the very low numbers of patients there is an expectation that the BIT will not exceed the £20m threshold''.* | Comments noted. The committee does take account of how its advice may enable the more efficient use of available healthcare resources. In general, the committee will want to be increasingly certain of the cost effectiveness of a technology as the impact of the adoption of the technology on NHS resources increases." (Please see section 6.2.14 of the Guide to the methods of technology appraisal 2013). A costing report and template will be available when the guidance is published. |
| 12 | Company | Immunocore Ltd. | *Page 3 – ''Clinical trial evidence suggests that tebentafusp could increase how long people live and the length of time before their cancer gets worse compared with the usual treatments offered, **but this is uncertain**.''*<br><br>We believe the statement that the clinical evidence is uncertain is inaccurate. As shown in the company submission, the interim analysis (October 2020) of study IMCgp100-202 showed the overall survival with tebentafusp was significantly longer than the comparator pembrolizumab: Overall survival at 1 year was 73% in the tebentafusp group and 59% in the control group (hazard ratio for death, 0.51; 95% confidence interval [CI], 0.37 to 0.71; P<0.001) in the intention-to-<br>treat population with a median OS of 21.7 months (18.6–28.6) for tebentafusp and 16 months (9.7–18.4) for the control group. | Comments noted. The FAD has been updated to reflect the committee's further consideration of the clinical evidence at the second committee meeting. Please see 3.7 and 3.8 of the FAD for its discussion and conclusions. |

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| | | | Additional data presented in the addendum accompanying this response demonstrate that more mature data from an April 2022 data cut of the clinical trial was consistent with this outcome: the overall survival in the tebentafusp arm was [redacted] [n=252] compared to [redacted] n=103] for the investigators choice arm. | |
| 13 | Company | Immunocore Ltd. | *Page 6 – The description of the MAO for tebentafusp is inaccurate*<br><br>• The protein gp100 is presented on the melanoma cell by HLA subtype. HLA is present on the surface of the target cancer cell, not the T cells, and the HLA protein presents a specific peptide of gp100 for binding by tebentafusp<br>• The tebentafusp effector domain (anti-CD3) binds to CD3 on T cells, to draw them in, forming the immune synapse with the gp100 peptide-HLA complex and directly killing the cancer cells | Comment noted. This description has been amended (please see section 3.3 of the FAD). |
| 14 | Company | Immunocore Ltd. | *Page 12 – ''The committee noted that most of the gains in overall survival made in the economic model are accumulated beyond the observed trial data. So the model is driven by the extrapolation of trial data, which is associated with uncertainty.''*<br><br>This statement that most of the gains in overall survival accumulated beyond the observed trial data, driven by the extrapolation which is associated with uncertainty, is not accurate. At the point of the August 2021 data-cut the number of events in the tebentafusp arm were [redacted] and in the investigators choice arm they were [redacted]. In addendum 2, data from the April 2022 is provided, showing consistent overall survival results with [redacted] events in the tebentafusp arm and [redacted] events in the investigators choice arm. Although not yet mature, the uncertainty in the OS extrapolation is significantly reduced in the updated analysis of the company based on the April 2022 data cut-off. Half of the QALY gain was captured over the trial follow-up (0-50 months) to further reduce the uncertainty in estimation of QALY gain. | Comment noted. The committee further considered the modelling of overall survival at the second committee meeting. Please see section 3.11 of the FAD for its conclusions. |
| 15 | Company | Immunocore Ltd. | *Page 9 & 16 – ''The committees preferred modelling assumption: using pembrolizumab in the model as the key comparator''*<br><br>Consistent with the NICE committee's recommendation, the cost-effective model has been updated based on a comparison of tebentafusp with pembrolizumab (Addendum 2). | Comments noted. The committee took these analyses into consideration at the second committee meeting. See section 3.5of the FAD. |
| 16 | Company | Immunocore Ltd. | *Page 12 & 16 – ''It considered that standard parametric curves should be the starting point for modelling and could be used for this treatment AND Page 13 - On balance using a standard parametric approach to extrapolate the data in both treatment arms was preferable.''*<br><br>We do not think that standard parametric approaches to extrapolate the data in both treatment arms would accurately model survival for tebentafusp beyond the trial period. The hazards plots of OS of tebentafusp and the IC arms are distinct, supporting using parametric models in the two arms. Furthermore, the biphasic characteristic of the | Comment noted. The committee further considered the modelling and extrapolation of modelling overall survival further at the second committee meeting. Please see section 3.11 of the FAD for its discussion and conclusions. |

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| | | | tebentafusp hazards, i.e., increase in hazards followed by a decrease in hazards, demonstrated a piecewise model was most suitable for modelling survival of tebentafusp in the updated base-case.<br>Therefore, the updated data from study IMCgp100-202 from the 04-April-2022 data cut support:<br>• Use of different parametric modelling of the tebentafusp and IC arms.<br>• Use of a piecewise model for the tebentafusp arm<br>Hazard plots of the pembrolizumab subgroup of the IC arm compared with the tebentafusp subgroup pre-selected for pembrolizumab prior to randomisation (termed tebentafusp PCP) are shown in Figure 1. The hazard plot of the pembrolizumab group approximates to a monotonic increasing hazard function, such as the Weibull. The shape of the hazard plot for the tebentafusp group is distinct to that of the pembrolizumab group. The shape of the tebentafusp hazard plot indicates two distinct phases, the first phase between 0 and 26 months is characterised by an increasing hazard and from 27 months onwards is characterised by a decreasing hazard. Taken together, the hazard plots support different modelling approaches for the pembrolizumab and tebentafusp groups.<br>The company acknowledges that standard parametric models, such as log-logistic can comprise a time-dependent mix of increasing hazard followed by decreasing hazard. However, the shape of the hazard plot of tebentafusp is distinct to that of a log logistic.<br>**Figure 1: Hazard plot for tebentafusp pre choice pembrolizumab (PCP) versus pembrolizumab**<br>  | |

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| 17 | Company | Immunocore Ltd. | *Page 13 & 16- ''It is not appropriate to include a 2-year stopping rule in the model''*<br><br>Consistent with the NICE committee's recommendation, the economic model has been updated and no longer includes a 2-year stopping rule (Addendum 2) | Comment noted. The committee acknowledged the updated model. It concluded that it was not appropriate to include a stopping rule in the model (see section 3.13 of the FAD). |
| 18 | Company | Immunocore Ltd. | *CDF section page 19 – ''overall survival data used in the economic model was highly uncertain''*<br><br>The statement that the overall survival data used in the economic model is ''highly uncertain'' is inaccurate, the hazard ratio of 0.51 (95% confidence interval [CI], 0.37 to 0.71; P<0.001) demonstrates this; overall survival rates at 12 months and 24 months for tebentafusp were 73.2% and 44.8%, respectively, and for investigator's choice were 58.5% and 20.3%, respectively, based on the October 2020 data cut-off. The updated data cut-off of April 2022 reduces any uncertainty in the OS, given the higher number of events observed. The results are consistent with previous cut-offs and demonstrate the robustness of the increase in survival with tebentafusp (See comment 2).<br><br>In addition, stated earlier in the document (page 12), the clinical experts specified the modelling of OS was plausible. | Comment noted. The committee further considered the clinical evidence, modelling and extrapolation of modelling overall survival,. Please see section 3.11 of the FAD for the committee discussions and conclusions. |
| 19 | Company | Immunocore Ltd. | *CDF section page 19 – contradiction of previous section*<br><br>On page 18 of the ACD it states that ERG's ICERs reflected the committees preferred assumptions more than the assumptions in the company's model, however the ERG's model did not contain the committee's assumption for the preferred comparator. Whereas the CDF section on page 19 states that *''the most plausible ICER is 250k''* without justification. This is not what the committee stated earlier in the document. The updated cost-effectiveness modelling provided in Addendum 2 now includes the committees preferred assumption of using pembrolizumab as the comparator and removing the 2-year stopping rule. | Comment noted. The committee considered the response to consultation and further analyses provided by the company at the second meeting. . It preferred the ERG analyse because the company's approach over-estimated the proportion of people surviving in the long term Its conclusions are reported in section 3.11 and 3.19 of the FAD. |
| 20 | Consultee | Melanoma Focus | The ACD decision reflects the committee's lack of confidence in the durability of benefit of treatment with tebentafusp. This is always a challenge when a new agent with a new mode of action is under appraisal.<br><br>We wish to draw the committee's attention to the following: | Comments noted. |
| 21 | Consultee | Melanoma Focus | The case for a substantial improvement in survival for patients with metastatic uveal melanoma treated with tebentafusp has been proved and is accepted by the committee. Lack of access to the only treatment which improves survival for this area of high unmet clinical need would mean that:<br>1. Patients treated in the NHS would die sooner than they need to<br>2. Patients treated in the private sector would live longer than NHS patients<br>3. The standard of care of patients in the NHS would fall well below many other western healthcare economies. | Comments noted. The committee considered further clinical evidence and the views of clinical experts and patient/carer representatives were further considered by the committee during the second committee meeting and when formulating its recommendations. |

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| 22 | Consultee | Melanoma Focus | We understand the company are providing additional data to the committee regarding longer term follow up of the phase I/II IMCgp100-102 patients. This may improve confidence in the durability of benefit experienced by some patients. We are also aware of many patients who remain on treatment after 2-3 years and are currently doing well.<br><br>Surely in a situation where clinical efficacy is proven but duration of benefit remains uncertain, the CDF would be an appropriate mechanism to allow access to patients of the only treatment that has been proved to improve survival for this disease whilst at the same time collecting data so that the durability of benefit can be assessed? | Comment noted. The committee acknowledged the additional information provided by the company and considered further clinical during the second committee meeting . Please see section 3.7 of the FAD for its discussion and conclusions regarding the clinical effectiveness data.. The committee tebentafusp did not meet the criteria to be considered for inclusion in the Cancer Drugs Fund (please see section 3.23 of the FAD). |
| 23 | Consultee | Melanoma Focus | It is not surprising that the shape of the KM curves for the tebentafusp and investigators choice populations are different. It is therefore reasonable to consider different models to best fit each curve. | Comment noted. The committee further considered the modelling and extrapolation of modelling overall survival, progression free survival and time on treatment. Please see section 3.11 and 3.12 of the FAD for the committee discussions and conclusions. |
| 24 | Web comment (public) | (Web commenter 1) | Tebentafusp does indeed bring hope. Tebentafusp has seen me go from 9 tumours in my lungs to being in a position where resection was possible. This was not at the beginning as it was on both lungs. At the moment I have no visible cancer as of my last scan 11 weeks ago. I am 48 and have been living with metastatic disease for the last 3 years. My results on Tebe are something my specialist nurse has not seen in the last 8 years of working with metastatic ocular melanoma, although my oncologist says it is soon to get excited. | Comment noted. Thank you for sharing your experience of tebentafusp. The committee considered all comments submitted as part of the consultation. It understood that tebentafusp could be a beneficial treatment. However the modelling was not without uncertainty and given the very high cost effectiveness estimates, the committee could not recommend tebentafusp. |
| 25 | Web comment (public) | (Web commenter 1) | Obviously we are very grateful for these treatments and will need these as only around half of patients have the right HLA. | Comment noted. Thank you. |
| 26 | Web comment (public) | (Web commenter 1) | As you have acknowledged there is no standard of care for ocular melanoma at the point of metastatic disease. However, it is my opinion that Tebentafusp should be standard of care for patients with the right HLA as it is targeted for our disease, hence the odds of it working increases. | Comment noted. Thank you. The committee considered all comments submitted as part of the consultation. It understood that tebentafusp could be a beneficial treatment. However the modelling was not without uncertainty and given the very high cost effectiveness estimates, the committee could not recommend tebentafusp. |
| 27 | Web comment (public) | (Web commenter 1) | There were people in their 20's on the trial. Admittedly ocular melanoma is usually older people but I was diagnosed with my primaries in my early 30's and my secondaries in my mid 40's. Through involvement in the community I have met others my age and younger so I think it is unfair to see this disease as something that just affects older people. Many of us are still working age and indeed still work through our diagnosis | Comment noted. Thank you. The committee carefully considered the and the views of clinical experts and patient/carer representatives further during the second committee meeting and when formulating its recommendations. |
| 28 | Web comment | (Web commenter 1) | This is exactly why it should be approved for those fit enough to use it. As ocular melanoma is a rare cancer it will be a small amount of people that need funding for this | Comment noted. Thank you. The committee considered all comments submitted as part of the |

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| | (public) | | so although I would imagine it is very expensive it is a small group of people who will need unlike if it was a more common cancer | consultation. It understood that tebentafusp could be a beneficial treatment. However the modelling was not without uncertainty and given the very high cost effectiveness estimates, the committee could not recommend tebentafusp. |
| 29 | Web comment (public) | (Web commenter 1) | When life span is so short 5.7 months is a very long time. It would make a huge difference to patients and their families | Comment noted. Thank you. The committee considered all comments submitted as part of the consultation. It understood that tebentafusp could be a beneficial treatment. However the modelling was not without uncertainty and given the very high cost effectiveness estimates, the committee could not recommend tebentafusp. |
| 30 | Web comment (public) | (Web commenter 1) | With a short life span the quality of life is very important and as noted the adverse reactions were more tolerable with Tebentafusp | Comment noted. Thank you. The committee considered all comments submitted as part of the consultation. It understood that tebentafusp could be a beneficial treatment. However the modelling was not without uncertainty and given the very high cost effectiveness estimates, the committee could not recommend tebentafusp. |
| 31 | Web comment (public) | (Web commenter 1) | As someone who has been taking Tebentafusp overt 2 years I appreciate this, as to stop a treatment that is working would be extremely stressful and seems unfair | Comment noted. Thank you for sharing your experience with tebentafusp. The committee considered all comments submitted as part of the consultation. It understood that tebentafusp could be a beneficial treatment. However the modelling was not without uncertainty and given the very high cost effectiveness estimates, the committee could not recommend tebentafusp. |
| 32 | Web comment (public) | (Web commenter 1) | I completely disagree with this decision and am really disappointed that ocular melanoma patients are being denied the most appropriate treatment for their disease. None of the drugs that have been proved most effective for our disease have been approved. | Comment noted. Thank you. The committee considered further clinical evidence and the views of clinical experts and patient/carer representatives were further considered by the committee during the second committee meeting. |
| 33 | Web comment (public) | (Web commenter 2) | The evidence regarding cutaneous melanoma has been presented. Unfortunately there is little evidence on uveal melanoma due to the rarity of the condition | Comment noted. Thank you. The committee considered further clinical evidence and the views of clinical experts and patient/carer representatives were further considered by the committee during the second committee meeting. |
| 34 | Web comment (public) | (Web commenter 2) | This is a very rare condition. As such the evidence submitted will never be as robust as a more common cancer. It therefore seems skewed to the disadvantage of these patients, especially when there is no alternative treatment available that gives tangible benefit. | Comment noted. Thank you. The committee considered further clinical evidence and the views of clinical experts and patient/carer representatives were further considered by the committee during the second committee meeting. |
| 35 | Web | (Web | Dear NICE committee | Comment noted. Thank you for providing this detail. |

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| | comment (public) | commenter 2) | I am writing on behalf of all UK Ocular Oncology Teams to express the collective support for the approval of Tebentafusp for the treatment of metastatic uveal melanoma. Uveal melanoma is a rare ocular cancer with an incidence of approximately 650 cases in the UK per year, managed by four supra-regional highly specialised units. The treatments for local disease within the eye are successful; however, approximately 50% of patients develop metastatic disease. Progress in the treatment of metastatic disease has been minimal over many decades. Chemotherapy and immunotherapy have shown very little benefit in terms of disease control or prolongation of life so that metastatic is almost always fatal. The treatment of metastatic uveal melanoma is not standardised.<br>Tebentafusp is the first systemic agent that has shown a significant benefit in a subgroup of patients with metastatic uveal melanoma. This is unmatched by any previous agents. We believe it to be groundbreaking in terms of its technological basis as well as patient outcomes. It gives our patients hope of treatment success with unparalleled medium-to-long-term outcomes. There are presently no alternative treatments.<br>I hope you may consider this in your review of the NICE application for this drug. The opinion of the UK ocular oncology community is unanimously in support of its use.<br>Yours faithfully,<br>  | The committee further considered clinical evidence, the views of patients and carers and clinical experts when having its discussions and forming its recommendation. |

NICE National Institute for Health and Care Excellence

**Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma [ID1441]**

**Consultation on the appraisal consultation document – deadline for comments** 5pm on Tuesday 12 July 2022. Please submit via NICE Docs.

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| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | Immunocore Ltd. |
| **Disclosure** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | **None** |
| **Name of commentator person completing form:** | [redacted] |
| | |

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NICE National Institute for Health and Care Excellence

**Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma [ID1441]**

**Consultation on the appraisal consultation document – deadline for comments** 5pm on Tuesday 12 July 2022. Please submit via NICE Docs.

| Comment number | Comments<br><br>Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| 1 | *Page 3 – ''Tebentafusp will be higher than an acceptable use of NHS resources''*<br><br>The NHS England Budget Impact Assessment (BIA) showed that due to the small number of patients, tebentafusp would be under the budget impact threshold set by the NHS. The Budget Impact Assessment by NHSE stated that ''*given the very low numbers of patients there is an expectation that the BIT will not exceed the £20m threshold''*. |
| 2 | *Page 3 – ''Clinical trial evidence suggests that tebentafusp could increase how long people live and the length of time before their cancer gets worse compared with the usual treatments offered,* ***but this is uncertain****.''*<br><br>We believe the statement that the clinical evidence is uncertain is inaccurate. As shown in the company submission, the interim analysis (October 2020) of study IMCgp100-202 showed the overall survival with tebentafusp was significantly longer than the comparator pembrolizumab: Overall survival at 1 year was 73% in the tebentafusp group and 59% in the control group (hazard ratio for death, 0.51; 95% confidence interval [CI], 0.37 to 0.71; P<0.001) in the intention-to-treat population with a median OS of 21.7 months (18.6–28.6) for tebentafusp and 16 months (9.7–18.4) for the control group.<br><br>Additional data presented in the addendum accompanying this response demonstrate that more mature data from an April 2022 data cut of the clinical trial was consistent with this outcome: the overall survival in the tebentafusp arm was [redacted] [n=252] compared to [redacted] [n=103] for the investigators choice arm. |
| 3 | *Page 6 – The description of the MAO for tebentafusp is inaccurate*<br><br>• The protein gp100 is presented on the melanoma cell by HLA subtype. HLA is present on the surface of the target cancer cell, not the T cells, and the HLA protein presents a specific peptide of gp100 for binding by tebentafusp<br>• The tebentafusp effector domain (anti-CD3) binds to CD3 on T cells, to draw them in, forming the immune synapse with the gp100 peptide-HLA complex and directly killing the cancer cells |
| 4 | *Page 12 – ''The committee noted that most of the gains in overall survival made in the economic model are accumulated beyond the observed trial data. So the model is driven by the extrapolation of trial data, which is associated with uncertainty.''* |

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**Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma [ID1441]**

**Consultation on the appraisal consultation document – deadline for comments** 5pm on Tuesday 12 July 2022. Please submit via NICE Docs.

| | |
|---|---|
| | This statement that most of the gains in overall survival accumulated beyond the observed trial data, driven by the extrapolation which is associated with uncertainty, is not accurate. At the point of the August 2021 data-cut the number of events in the tebentafusp arm were [redacted] and in the investigators choice arm they were [redacted]. In addendum 2, data from the April 2022 is provided, showing consistent overall survival results with [redacted] events in the tebentafusp arm and [redacted] events in the investigators choice arm. Although not yet mature, the uncertainty in the OS extrapolation is significantly reduced in the updated analysis of the company based on the April 2022 data cut-off. Half of the QALY gain was captured over the trial follow-up (0-50 months) to further reduce the uncertainty in estimation of QALY gain. |
| 5 | *Page 9 & 16 – ''The committees preferred modelling assumption: using pembrolizumab in the model as the key comparator''*<br><br>Consistent with the NICE committee's recommendation, the cost-effective model has been updated based on a comparison of tebentafusp with pembrolizumab (Addendum 2). |
| 6 | *Page 12 & 16 – ''It considered that standard parametric curves should be the starting point for modelling and could be used for this treatment AND Page 13 - On balance using a standard parametric approach to extrapolate the data in both treatment arms was preferable.''*<br><br>We do not think that standard parametric approaches to extrapolate the data in both treatment arms would accurately model survival for tebentafusp beyond the trial period. The hazards plots of OS of tebentafusp and the IC arms are distinct, supporting using parametric models in the two arms. Furthermore, the biphasic characteristic of the tebentafusp hazards, i.e., increase in hazards followed by a decrease in hazards, demonstrated a piecewise model was most suitable for modelling survival of tebentafusp in the updated base-case.<br>Therefore, the updated data from study IMCgp100-202 from the 04-April-2022 data cut support:<br>• Use of different parametric modelling of the tebentafusp and IC arms.<br>• Use of a piecewise model for the tebentafusp arm<br>Hazard plots of the pembrolizumab subgroup of the IC arm compared with the tebentafusp subgroup pre-selected for pembrolizumab prior to randomisation (termed tebentafusp PCP) are shown in Figure 1. The hazard plot of the pembrolizumab group approximates to a monotonic increasing hazard function, such as the Weibull. The shape of the hazard plot for the tebentafusp group is distinct to that of the pembrolizumab group. The shape of the tebentafusp hazard plot indicates two distinct phases, the first phase between 0 and 26 months is characterised by an increasing hazard and from 27 months onwards is characterised by a decreasing hazard. Taken |

| | |
|---|---|
| | together, the hazard plots support different modelling approaches for the pembrolizumab and tebentafusp groups.<br><br>The company acknowledges that standard parametric models, such as log-logistic can comprise a time-dependent mix of increasing hazard followed by decreasing hazard. However, the shape of the hazard plot of tebentafusp is distinct to that of a log logistic.<br><br>**Figure 1: Hazard plot for tebentafusp pre choice pembrolizumab (PCP) versus pembrolizumab**<br>  |
| 7 | *Page 13 & 16- ''It is not appropriate to include a 2-year stopping rule in the model''*<br><br>Consistent with the NICE committee's recommendation, the economic model has been updated and no longer includes a 2-year stopping rule (Addendum 2) |
| 8 | *CDF section page 19 – ''overall survival data used in the economic model was highly uncertain''*<br><br>The statement that the overall survival data used in the economic model is ''highly uncertain'' is inaccurate, the hazard ratio of 0.51 (95% confidence interval [CI], 0.37 to 0.71; P<0.001) demonstrates this; overall survival rates at 12 months and 24 months for tebentafusp were 73.2% and 44.8%, respectively, and for investigator's choice were 58.5% and 20.3%, respectively, based on the October 2020 data cut-off. The updated data cut-off of April 2022 reduces any uncertainty in the OS, given the higher number of events observed. The results are consistent with previous cut-offs and demonstrate the robustness of the increase in survival with tebentafusp (See comment 2).<br><br>In addition, stated earlier in the document (page 12), the clinical experts specified the modelling of OS was plausible. |

NICE National Institute for Health and Care Excellence

**Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma [ID1441]**

**Consultation on the appraisal consultation document – deadline for comments** 5pm on Tuesday 12 July 2022. Please submit via NICE Docs.

| | |
|---|---|
| 9 | *CDF section page 19 – contradiction of previous section*<br><br>On page 18 of the ACD it states that ERG's ICERs reflected the committees preferred assumptions more than the assumptions in the company's model, however the ERG's model did not contain the committee's assumption for the preferred comparator. Whereas the CDF section on page 19 states that '*"the most plausible ICER is 250k"* without justification. This is not what the committee stated earlier in the document. The updated cost-effectiveness modelling provided in Addendum 2 now includes the committees preferred assumption of using pembrolizumab as the comparator and removing the 2-year stopping rule. |

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single technology appraisal

## Addendum 2: Technical engagement response update of Document B3

## Company evidence submission

**30th September 2022**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| **NICE_ID1441_ Addendum 2: Update of Document B3_redacted** | **V 1** | **Yes** | **30th September 2022** |

The model accompanying addendum 2 will be submitted separately

Appendices J, L and M are included in the document

Appendix K: Checklist of confidential information, will be submitted separately

# Abbreviations

| | |
|---|---|
| ACD | Appraisal Committee Documents |
| CEM | Cost-effectiveness model |
| CRS | Cytokine release syndrome |
| DCO | Data cut-off |
| HR | Hazard ratio |
| IA1 | First interim analysis |
| IC | Investigator's choice |
| ICER | Incremental cost-effectiveness ratio |
| ITT | Intention to treat |
| KM | Kaplan-Meier |
| LDH | Lactate dehydrogenase |
| NICE | National Institute for Health and Care Excellence |
| OS | Overall survival |
| PAS | Patient access scheme |
| PCP | Pre-choice pembrolizumab |
| PFS | Progression-free survival |
| PSA | Probabilistic sensitivity analysis |
| QALY | Quality-adjusted life years |
| TTD | Time-to-treatment discontinuation |
| ULN | Upper limit of normal |

# NICE ADDENDUM

The Addendum is part of the response to the NICE ACD ID1441.

## Summary

The cost-effectiveness model (CEM) was updated to incorporate (i) the comparator and modelling as preferred by the committee in the ACD and (ii) updated data of study IMCgp100-202 (NCT03070392) (data cut date: 04 April 2022).

The addendum includes updates for:

- Comparator and population
- Clinical data
- Extrapolation analysis
- Other model updates
- Updated cost-effectiveness results (section B.3 of the submission dossier)

Other modelling parameters remained unchanged from addendum 1 (25 April 2022) and are detailed in Appendix M: model updates from Addendum 1 (25 April 2022) retained in Addendum 2 (30 September 2022).

### *Summary of key model updates*

Comparator and population

Consistent with the NICE committee's recommendation, the cost-effective modelling was based on a comparison of tebentafusp with pembrolizumab.

A comparison of tebentafusp with pembrolizumab that minimises imbalance of prognostic variables requires restricting the tebentafusp group to the subgroup of patients who were pre-selected to receive pembrolizumab prior to randomisation ["pre-choice pembrolizumab"; (PCP)]. For instance, lactate dehydrogenase (LDH) level is an important prognostic factor in metastatic uveal melanoma, above the

upper limit of normal (ULN) is associated with worse prognosis and survival [1]. In study IMCgp100-202, a higher proportion of patients pre-selected to receive dacarbazine (both arms combined) had a LDH level above the ULN than patients preselected for pembrolizumab, whilst the inverse was evident for patients preselected for ipilimumab. A similar pattern was also evident for tumour size (Table 3). In summary, the prognostic variables for patients preselected for dacarbazine or ipilimumab was different to patients pre-selected for pembrolizumab prior to randomization.

A balanced comparison of tebentafusp with pembrolizumab requires restricting the tebentafusp group to the subgroup of patients who were pre-selected to receive pembrolizumab prior to randomisation ["pre-choice pembrolizumab"; (PCP)].

Extrapolation analysis

Kaplan-Meier (KM) plots for overall survival (OS) and hazard plots for: (i) the intention-to-treat (ITT) analysis set, tebentafusp versus Investigator's choice (IC), and (ii) tebentafusp PCP versus pembrolizumab are shown in

The updated data from study IMCgp100-202 supports:

- Use of a different parametric models for tebentafusp and pembrolizumab.
- Use of a piecewise model for the tebentafusp arm

## *Model results summary*

The cost per quality-adjusted life-years (QALYs) of tebentafusp with the updated company base case is [redacted] per QALY.

The mean treatment duration of tebentafusp was updated in the NHSE/I budget impact model to reflect the latest available data of 04 April 2022, [redacted] months (tebentafusp ITT). Additionally, treatment adherence to tebentafusp of 92% was applied to both tebentafusp acquisition costs and administration costs, reflecting two interruptions of two weeks, with minimal impact on the safety or efficacy of tebentafusp [2]. Details on treatment compliance are presented in section Treatment

adherence. Based on the updated NHSE/I budget impact model, the total drug costs for tebentafusp with the patient-access scheme (PAS) are [redacted] at year 3 when uptake reaches 50% and are within the threshold for the NHSE budget impact test.

Figure 1. The shape of the KM plots and hazard plots is similar for both comparisons, principally due to pembrolizumab being the major IC treatment selected from the investigator's' choice prior to randomisation for [redacted] in the tebentafusp arm, 103 of 126 (82%) in the IC] of the patients enrolled in study IMCgp100-202. All patients pre-selected to pembrolizumab who were subsequently randomised to the IC arm received pembrolizumab. The hazard plots demonstrate that the change in hazards over time for the tebentafusp arm is distinctly different to the IC arm. The hazard plot for the IC arm increases with time monotonically. In contrast, the hazard plot with tebentafusp has two phases, first increasing and then decreasing which corresponds to the elongation of the KM plot of tebentafusp.

The updated data from study IMCgp100-202 supports:

- Use of a different parametric models for tebentafusp and pembrolizumab.
- Use of a piecewise model for the tebentafusp arm

## *Model results summary*

The cost per quality-adjusted life-years (QALYs) of tebentafusp with the updated company base case is [redacted] per QALY.

The mean treatment duration of tebentafusp was updated in the NHSE/I budget impact model to reflect the latest available data of 04 April 2022, [redacted] months (tebentafusp ITT). Additionally, treatment adherence to tebentafusp of 92% was applied to both tebentafusp acquisition costs and administration costs, reflecting two interruptions of two weeks, with minimal impact on the safety or efficacy of tebentafusp [2]. Details on treatment compliance are presented in section Treatment adherence. Based on the updated NHSE/I budget impact model, the total drug costs for tebentafusp with the patient-access scheme (PAS) are [redacted] at

year 3 when uptake reaches 50% and are within the threshold for the NHSE budget impact test.

**Figure 1. Kaplan Meier curve (left) and hazard plot (right), ITT (top) and tebentafusp PCP vs. pembrolizumab (bottom)**

# Comparator and population

## *Control (IC) arm*

Consistent with the recommendation of the NICE committee (ACD 21 June 2022), cost-effective modelling was based on a comparison of tebentafusp with pembrolizumab.

Cross-over from the IC to tebentafusp was allowed after the primary endpoint was met at the first interim analysis (IA1). Cross-over was not specified in the protocol and required a specific amendment to the protocol. Therefore, the time between disease progression and cross-over to tebentafusp or time between the IA1 and cross-over was likely subject to significant variation independent of specific patient demographics, disease characteristics or treatment. Between the data-cut-off (DCO) at IA1 of 13 October 2020 and 04 April 2022 (most recent DCO), [redacted] patients had crossed over from pembrolizumab to tebentafusp.

The analysis of the survival endpoints for the pembrolizumab subgroup of the IC arm was not adjusted for cross-over because:

- There were too few patients (n=[redacted]) who crossed over to tebentafusp to support a statistical analysis and adjustment for differences between patients who crossed over and those that did not.
- Cross over was not mandated in the protocol so there was no clinical rule for determining the time of cross over, which would have produced significant additional uncertainty in an adjustment for cross-over, as stated above.

All patients who crossed-over from the IC treatment to tebentafusp had confirmed disease progression and discontinued treatment at the time of cross-over. Hence, the impact of cross-over is limited to OS. The impact of cross-over on estimation of OS was evaluated according to two scenarios, which were implemented in the model. In the first scenario, the patients are censored at the point of cross-over (only impacts OS), and in a second scenario patients who crossed-over are excluded from

the analysis. KM plots for the ITT of the IC arm and two scenarios for the IC pembrolizumab subgroup are shown in Figure 2 and the median OS results for each are shown in Table 1. The KM plots for the IC pembrolizumab subgroup overlaps with the KM plot of the subgroup of pembrolizumab with censoring at the time of cross-over. The median OS is identical for the two subgroups. In conclusion, censoring at the time of cross-over is highly unlikely to impact analysis of OS compared to not including adjustment for cross-over from pembrolizumab to tebentafusp post-progression after the first interim analysis.

**Figure 2. Kaplan Meier plot of overall survival investigator's choice arm and pembrolizumab subgroups April 2022 DCO**

Pembro, all patients who received pembrolizumab. Pembro no cross-over, patients who received tebentafusp after pembrolizumab excluded. Pembro censored, patients who received tebentafusp after pembrolizumab censored at the time they received tebentafusp.

**Table 1. Median (95% confidence interval) overall survival investigator's choice and pembrolizumab subgroups 04 April 2022 data cut-off**

| Population | 04 April 2022<br>Months (95% CI) |
|---|---|

| | |
|---|---|
| IC (n=126) | [redacted] |
| Pembrolizumab (n=103) | [redacted] |
| Pembrolizumab censored at cross-over (n=103) | [redacted] |
| Pembrolizumab with exclusion of patients who crossed-over (n=89) | [redacted] |

Analysis of OS for the pembrolizumab sub-group with exclusion of patients who crossed over to tebentafusp resulted in a median OS of [redacted] months [redacted], which is lower (by [redacted] months) than the pembrolizumab sub-group with or without censoring at cross-over.

Censoring at cross-over resulted in minimal impact on OS as demonstrated in Figure 2 and Table 1. The impact on the ICER is expected to be minimal. Hence, the model base case used the pembrolizumab subgroup, not censoring at cross-over to use all the OS data available for the pembrolizumab subgroup (i.e., including survival follow-up when patients had crossed-over from pembrolizumab to tebentafusp). The impact of censoring at cross-over on the ICER is presented in scenario analysis (Table 25).

### *Tebentafusp arm*

As explained above, prior to randomisation to either tebentafusp or the IC arm in study IMCgp100-202, patients were assigned to receive one of the three regimens of the IC (pembrolizumab, ipilimumab and dacarbazine)(Table 2) [3]. All patients randomised to the IC arm received the pre-selected treatment and patients randomized to the intervention arm received tebentafusp (responses to the clarification questions B4 and B5, December 2021).

**Table 2. Pre-selected treatment from Investigator's Choice prior to randomisation**

| | **IC** | **Tebentafusp** |
|---|---|---|

| | | |
|---|---|---|
| Pembrolizumab | 103* | 199 |
| Ipilimumab | 16* | 40 |
| Dacarbazine | 7* | 13 |
| *Note: All patients randomised to the IC arm received the regimen selected prior to randomisation<br>Source: CSR IMCgp100-202 [3] | | |

Hence, the choice of IC was known for patients who received tebentafusp and enabled matching of patients based on pre-selection of the treatment included in the IC and control for difference in disease patient demographic or disease characteristics (Table 3).

For instance, lactate dehydrogenase (LDH) level is an important prognostic factor in metastatic uveal melanoma, above the upper limit of normal (ULN) is associated with worse prognosis and survival [1]. In study IMCgp100-202, a higher proportion of patients pre-selected to receive dacarbazine (both arms combined) had LDH level above the ULN, than patients preselected for pembrolizumab, which is an important prognostic factor for metastatic uveal melanoma [1]. The inverse was evident for patients preselected for ipilimumab. A similar pattern was also evident for tumour size (Table 3). In summary, the prognostic variables for patients preselected for dacarbazine or ipilimumab was different to patients pre-selected for pembrolizumab prior to randomization.

**Table 3. Summary of baseline disease characteristics by investigator pre-choice of therapy in Intent-to-Treat population 04 April 2022 data cut off**

| | **Dacarbazine (N=20)** | **Ipilimumab (N=56)** | **Pembrolizumab (N=302)** |
|---|---|---|---|
| **Baseline LDH** | | | |
| LDH =< ULN 250 U/L (n, %) | [redacted] | [redacted] | [redacted] |
| **LDH > ULN 250 U/L (n, %)** | [redacted] | [redacted] | [redacted] |
| n | [redacted] | [redacted] | [redacted] |

| | Dacarbazine (N=20) | Ipilimumab (N=56) | Pembrolizumab (N=302) |
|---|---|---|---|
| Mean (SD) | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Min, Max | [redacted] | [redacted] | [redacted] |
| **Baseline Largest Metastatic Lesion** | | | |
| **<= 3cm** | [redacted] | [redacted] | [redacted] |
| 3.1-8.0 cm | [redacted] | [redacted] | [redacted] |
| >=8.1 cm | [redacted] | [redacted] | [redacted] |
| n | [redacted] | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Min, Max | [redacted] | [redacted] | [redacted] |
| **Baseline Largest Liver Lesion** | | | |
| **< 3 cm** | [redacted] | [redacted] | [redacted] |
| >= 3 cm | [redacted] | [redacted] | [redacted] |
| No liver lesion | [redacted] | [redacted] | [redacted] |
| n | [redacted] | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Min, Max | [redacted] | [redacted] | [redacted] |

In conclusion, the appropriate comparison of tebentafusp versus pembrolizumab for the base case should include only the subgroup of patients in the tebentafusp arm pre-selected to receive pembrolizumab prior to randomisation, termed “pre-choice pembrolizumab” (PCP) sub-group.

# Clinical data

## *Study IMCgp100-202*

An updated data cut-off (DCO) is provided (04 April 2022) for OS and time to treatment discontinuation (TTD). Data on progression-free survival (PFS) were not

collected. PFS data were considered mature at the previous data cut-off of 12 August 2021, with [redacted] PFS events in the tebentafusp arm and [redacted] in the IC arm.

**Intention to treat analysis set**

***Overall survival***

KM plots of OS for the intention-to-treat (ITT) analysis set are presented in Figure 3, and median OS are compared with the two earlier DCOs (Table 4). Of 126 patients in the IC arm, there were [redacted] deaths and [redacted] patients censored in the DCO of 04-April 2022. There were no significant differences in median OS.

**Figure 3 Kaplan Meier curve of overall survival for study IMCgp100-202 Intention to treat analysis set from 04-April-2022 DCO**

**Table 4. Median (95% CI) overall survival intent-to-treat set all data cut-offs**

| | **13 October 2020** | **12 August 2021** | **04 April 2022** |
|---|---|---|---|
| **Tebentafusp (n=252)** | 21.7 (18.6-28.6) | [redacted] | [redacted] |
| **Investigator's choice (n=126)** | 16.0 (9.7-18.4) | [redacted] | [redacted] |

***Time to treatment discontinuation***

KM plots of TTD for the ITT analysis set are presented in Figure 4 and the median TTD for the three DCOs are shown in Table 5. In the tebentafusp arm, [redacted] patients discontinued treatment, and [redacted] discontinued treatment in the IC arm. The TTD data may be considered mature and supports a robust estimation for cost of both treatments.

**Figure 4 Kaplan Meier curve of time to treatment discontinuation (TTD) for study IMCgp100-202 Intention to treat analysis set 04-April-2022 data cut-off**

**Table 5. Median (95% confidence interval) time to treatment discontinuation intent-to-treat set all data cut-offs**

| | **13-October-2020** | **12-August-2021** | **04-April-2022** |
|---|---|---|---|
| **Tebentafusp (n=252)** | 5.6 (5.3-7.6) | [redacted] | [redacted] |
| **Investigator's choice (n=126)** | 2.1 (2.1-2.8) | [redacted] | [redacted] |

**Tebentafusp and pembrolizumab subgroups**

Table 6 presents the stratified hazard ratio (HR) for the ITT analysis for the three data sets (DCOs) and the subgroups analysed from the DCO of 04-April-2022. Specifically, the HR for the tebentafusp PCP subgroup versus the pembrolizumab subgroups of the IC arm (pembrolizumab, pembrolizumab censored at cross-over and pembrolizumab excluding patients who crossed-over) for the April 2022 DCO are shown. The HR for the tebentafusp PCP subgroup versus pembrolizumab (base case) was similar (HR=[redacted]) to the ITT analysis (HR=[redacted]) and the HR for tebentafusp PCP subgroup versus pembrolizumab subgroup with exclusion of patients who crossed over to tebentafusp (HR=[redacted]) was lower than the base case. Therefore, the base case may be considered a conservative approach for modelling cost-effectiveness of tebentafusp versus pembrolizumab.

**Table 6. Hazard ratio for different data cut-offs and comparators (Base case is shaded grey)**

| Comparator | HR (95% CI) |
|---|---|
| **Tebentafusp (n=252) vs. IC (n=126) 13 October 2020 (including cross-over)** | 0.51 (0.37, 0.71) |
| **Tebentafusp (n=252) vs. IC (n=126) 12 August 2021 (including cross-over)** | [redacted] |
| **Tebentafusp (n=252) vs. IC (n=126) (including cross-over)** | [redacted] |
| **Tebentafusp (n=252) vs. Pembrolizumab (including cross-over) (n=103)** | [redacted] |
| **Tebentafusp (n=252) vs. Pembrolizumab, censored at cross-over (n=103)** | [redacted] |
| **Tebentafusp (n=252) vs. Pembrolizumab, with exclusion of patients who crossed-over (n=89)** | [redacted] |

| | |
|---|---|
| **Tebentafusp PCP (n=199) vs Pembrolizumab (n=103)** | [redacted] |
| **Tebentafusp PCP (n=199) s Pembrolizumab, censored at cross-over (n=103)** | [redacted] |
| **Tebentafusp PCP (n=199) vs Pembrolizumab, with exclusion of patients who crossed-over (n=89)** | [redacted] |
| Note: Data cut 04-April-2022 unless stated otherwise<br>PCP; pre-choice pembrolizumab | |

### *Study IMCgp100-102*

The follow up of the single-arm study IMCgp100-102 (NCT02570308) was longer than study IMCgp100-202. Although study IMCgp100-102 included patients who had received at least one prior therapy, the OS results may be used to inform modelling and clinical plausibility of longer-term survival with tebentafusp from study IMCgp100-202.

Overlayed KM plots of OS for three dates (20-March-2020, 31-March-2021 and 04-April-2022) are shown in Figure 5. Data collected on 04-April-2022 represents 3-year follow up. Elongation of the OS KM curve for the longest follow up (04-April 2022) is evident with a survival probability of [redacted] at 36 months and [redacted] at 48 months (Table 7).

**Figure 5. Study IMCgp100-102 Overall survival from the different data cut-offs - All patients (N=146)**

**Table 7. Landmark survival IMCgp100-102 (N=146) 04 April 2022**

| Time (months) | Survival | Failure | Standard Error | Number Failed | Number Left |
|---|---|---|---|---|---|
| 12 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 24 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 36 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 48 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

The survival from study IMCgp100-102 compares favourably with historical data for treatments used as second line or later published by Rantala et al. [4], reporting

survival of 34% at one year, 14% at two years and 5% at three years for patients treated with checkpoint inhibitors, such as pembrolizumab.

# Extrapolation analysis

The extrapolation analysis is presented for the base case comparing the tebentafusp sub-group pre-selected choice of pembrolizumab (PCP) with the pembrolizumab sub-group of the IC arm.

## *Overall Survival*

### Kaplan-Meier data

KM plots for the tebentafusp PCP subgroup and the pembrolizumab subgroup of the IC arm are shown Figure 6.

**Figure 6. Kaplan Meier curve of overall survival for study IMCgp100-202 tebentafusp pre-choice pembrolizumab and pembrolizumab 04-April 2022 data cut-off**

The KM plot for tebentafusp is characterised by two phases. First the survival probability rapidly decreases with time [redacted]. In the second phase [redacted], the plot elongates and the survival probability decreases more slowly over time. Elongation of the KM data of tebentafusp is characterised by a change in the

hazards and two distinct phases of the hazards plot (Figure 7). The hazards plot increases monotonically from [redacted] and decreases from [redacted] onwards. This biphasic characteristic of the KM plot and hazards plot is present in both the ITT group treated with tebentafusp and the sub-group pre-selected to receive pembrolizumab if randomised to tebentafusp (i.e., the tebentafusp-PCP subgroup) (Figure 1).

In contrast, the KM plots and hazard plots of OS for the IC arm, both ITT and the pembrolizumab subgroup, are characterised by a monotonic increasing hazard i.e., the longer the survival the higher the risk of death (Figure 7 and Figure 1).

**Modelling approach**

The distinct hazards plots of OS between tebentafusp and the IC arms demonstrate that the parametric models for modelling KM survival of each are different. Furthermore, the biphasic characteristic of the tebentafusp OS data, i.e., increase in hazards followed by a decrease in hazards demonstrated a piecewise model was most suitable for modelling survival of tebentafusp.

Therefore, the updated data from study IMCgp100-202 from 04-April-2022 support:

- Use of a different parametric modelling of the tebentafusp and IC arms.
- Use of a piecewise model for the tebentafusp arm

Hazard plots of the pembrolizumab subgroup of the IC arm compared with the tebentafusp PCP subgroup are shown in Figure 7. The hazard plot of the pembrolizumab group approximates to a monotonic increasing hazard function, such as the Weibull. The shape of the hazard plot for the tebentafusp group is distinct to that of the pembrolizumab group.

The shape of the tebentafusp hazard plot indicates two distinct phases, the first phase between [redacted] is characterised by an increasing hazard and from [redacted] onwards is characterised by a decreasing hazard. Taken together, the hazard plots support different modelling approaches for the pembrolizumab and tebentafusp groups.

The company acknowledges that standard parametric models, such as log-logistic can comprise a time-dependent mix of increasing hazard followed by decreasing hazard. However, the shape of the hazard plot of tebentafusp is distinct to that of a log logistic.

**Figure 7: Hazard plot for tebentafusp pre choice pembrolizumab (PCP) versus pembrolizumab**

***Tebentafusp pre-choice pembrolizumab (PCP) extrapolation analysis***

Consistent with the biphasic hazards plot of tebentafusp, the company adopted a piecewise model for modelling OS [5], using the KM data for the first phase (increasing hazard) and standard parametric model for the second phase (decreasing hazard) to create a complete survival function.

There are no statistics for choosing the time point at which to split the dataset, and guidance in the NICE TSD 21 on flexible model is limited [5]. The choice is driven by visual inspection of the hazards plot, to identify time-points where there is sufficient change in the hazard to warrant fitting a different model.

The plot of hazards peaks at [redacted] (Figure 7) and changes rapidly between [redacted]. Fitting a parametric model in the region where the hazard changes

rapidly with time may result in poorly fitting models using standard parametric models. Therefore, to model survival more accurately, the KM curve was used up to the point from which the hazards is monotonically decreasing [redacted], beyond which a standard parametric model was used to estimate survival over the long-term. Additionally, during the first phase [redacted], the Kaplan-Meier data from the study is mature with limited censoring [[redacted] patients censored out of [redacted]].

In the base-case, the dataset was split at [redacted], the point from which the hazard is monotonically decreasing. Sensitivity analyses for the impact on the ICER were conducted at: (i) [redacted], the peak of the hazard, and (ii) [redacted], the mid-point between the peak and when the change to decreasing hazards is established.

Consistent with the recommendation from NICE (ACD section 3.10) and the NICE TSD 21 on flexible methods for survival analysis [5], the company adopted standard parametric models for modelling the second phase (beyond [redacted] months) of the survival data. The modelled survival produced by the parametric model was adjusted for background mortality to ensure clinically plausibility of survival modelled beyond the duration of observed data, using life tables for England 2018-2020 from the Office for National Statistics [6]. The lognormal model was preferred because of its fitting estimators, its property to capture long-term survival and clinical plausibility. The company's base case estimation of OS uses the piecewise approach with (i) KM data between [redacted] months and (ii) lognormal distribution beyond [redacted] months. This approach was consistent with previous NICE TAs, such as TA519 for pembrolizumab, which a lognormal model was attached to a pre-determined point of the Kaplan Meier survival function. Other TAs that use a similar piecewise approach are described in the NICE TSD 21 [5].

The base case modelling of survival over 5-years and 10-years using the piecewise model (KM + log-normal) for the tebentafusp PCP sub-group are overlaid with observed KM data (Figure 8) and compared with modelling with the log-normal model fitted to the complete PCP subgroup dataset. Visual inspection shows that the

piecewise model provides the best fit to the data and clinically plausible long-term survival.

As acknowledged in the ACD using the prior modelling approach (i.e., 3-knot spline), "*The clinical experts explained that the overall survival estimates from the company's model were plausible*". The overall survival estimates from the company's preferred piecewise approach described herein are clinically plausible and more robust because the estimates are calculated on observed data with longer follow up (i.e., data cut of 04-April-2022).

The impact of using different standard parametric models on the ICER with the piecewise approach were evaluated in sensitivity analyses, as were the full parametric model approach. Results of survival modelling using the piecewise models with the six standard parametric models are shown in Table 9.

Using the Company base case, the QALY gain with tebentafusp beyond the observed data are [redacted] of the total QALY gain (discounted) (Table 8), hence half of the QALY gain is accrued over the trial follow-up, and thus associated with limited uncertainty.

**Table 8. QALYs and LYs gains over the trial follow-up and modelled time horizon**

| | **Life-years gained (discounted)** | **QALYs gains (discounted)** |
|---|---|---|
| **Trial follow-up (KM data)** | [redacted] | [redacted] |
| **Lifetime horizon (modelled)** | [redacted] | [redacted] |
| **% beyond observed data** | [redacted] | [redacted] |

**Figure 8 Overlay of KM curve (04 April 2022 DCO), piecewise models (KM + log-normal) (left) or log-normal (right) for tebentafusp pre-choice pembrolizumab (PCP), 5-year (top) and 10-year time horizon (bottom)**

**Table 9. OS piecewise modes (KM curve + standard parametric model) for tebentafusp pre-choice pembrolizumab 04 April 2022 DCO**

| Months | KM April 2022 DC) | Exponential | Weibull | Lognormal | Log-logistic | Gompertz | Generalised gamma |
|---|---|---|---|---|---|---|---|
| **AIC** | | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **BIC** | | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Ranking based on AIC and BIC** | | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 6 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 9 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 12 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 18 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 24 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 30 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 36 (3 years) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 48 (4 years) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 60 (5 years) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 120 (10 years) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

KM data from the trial is used to estimate survival from [redacted] months. Lognormal model applied from [redacted] months.
Modelled observed period (light grey) and estimated survival beyond trial period (dark grey) are highlighted from 30-120 months.

***Pembrolizumab subgroup of IC extrapolation analysis***

Consistent with the company's prior submission, the Weibull model was used to estimate survival with pembrolizumab.

The KM plots of OS for pembrolizumab and survival modelled with a Weibull distribution are overlayed with survival data from first-line (1L) treatments published by Rantala et al. [4], and shown in Figure 9 for each of the three data cuts. Based on comparison with historical data (Figure 9 and Table 10), the Weibull model provides the most clinically plausible estimation of long-term survival and is likely a conservative approach to modelling long-term survival with possible over-estimation of survival, between 6 and 48 months, compared to historical data for treatments used in the first line setting. As highlighted in Table 10, the 1-year, 3-year and 5-year survival probabilities of the Weibull model are conservative compared to the data published by Rantala et al [4].

**Figure 9. Overlay of KM Rantala 1L, KM pembrolizumab and fitted Weibull model, overall survival, 04-April 2022 DCO and 13-October 2020 DCO**

All alternative models provided a good fit to the observed data based on AIC and BIC (Table 10), with less than 1% difference in AIC and BIC between all models. The choice of model was therefore driven by the clinically plausibility of long-term extrapolation of survival by comparison with published historical data (Table 10) [4] and presented in the Company submission. The log-normal, log-logistic and generalised gamma models are not considered clinically plausible because the 5-year survival probability is greater than 10% and excessive compared to 3% survival at 5 years (Table 10, highlighted) for treatments used in first line according to the meta-analysis by Rantala et al. [4]. The Weibull model provided a good fit to the observed data and the most clinically plausible 5-year survival compared to published historical data [4].

**Table 10. OS parametric models Pembrolizumab 04 April 2022 DCO vs KM curve and Rantala et al first line**

| Months | KM April 2022 DCO | Rantala 1L | Exponential | Weibull | Lognormal | Log-logistic | Gompertz | Generalised gamma |
|---|---|---|---|---|---|---|---|---|
| **AIC** | | | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **BIC** | | | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Ranking based on AIC and BIC** | | | 2 | 4 | 1 | 2 | 6 | 4 |
| 6 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 9 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 12 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 18 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 24 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 30 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 36 (3 years) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 48 (4 years) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 60 (5 years) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 120 (10 years) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion

## *Progression-free survival (PFS)*

Data for PFS were not collected in the 04-April 2022 data cut because PFS was mature in the prior data cut of 12 August 2021 in which the number of PFS events was [redacted] out of 256 patients for the tebentafusp ITT group and [redacted] out of 126 in the investigators' choice arm.

Modelling of PFS remains unchanged from the original Company base case. Modelling of PFS is based on data from 12 August 2021 using the piecewise model with KM data and extrapolation using the generalised gamma function.

For the base-case, the tebentafusp PCP subgroup and pembrolizumab subgroup were used.

## *Time to treatment discontinuation*

### *Kaplan-Meier data*

Data for time on treatment was updated in the economic model with the 04-April 2022 data set. KM plots for the tebentafusp PCP subgroup and pembrolizumab are shown in Figure 10. In the tebentafusp PCP subgroup, [redacted] events out of 192 patients were observed, and [redacted] out of 91 in the pembrolizumab arm were observed. Data for TTD for both groups are considered mature.

**Figure 10. KM curve time to treatment discontinuation tebentafusp PCP and pembrolizumab 04-April 2022 DCO**

***Modelling approach***

Since NICE considered the piecewise approach previously presented by the company for treatment duration, this approach was retained for the analysis of the updated treatment duration data from the data cut of 04-April 2022. Specifically, the exponential distribution, with a switch from the KM curve at 25% of patients at risk in the tebentafusp PCP arm and 15% in the pembrolizumab arm. The fitted models are presented in Figure 11, and the proportion of patients on treatment with tebentafusp PCP and pembrolizumab modelled and observed in the trial are presented in Table 11**Error! Reference source not found.**.

**Figure 11. Piecewise model with Kaplan Meier curve and exponential model 04-April 2021 DCO**

**Table 11. Time-to-treatment discontinuation KM data, exponential extrapolation and piecewise model using Kaplan-Meier curve plus exponential tail 04 April 2022 data cut-off**

| | Tebentafusp PCP (n=193) | | | Pembrolizumab (n=91) | | |
|---|---|---|---|---|---|---|
| | KM (%, #risk) | Exponential | Piecewise model (base case) | KM (%, #risk) | Exponential | Piecewise (base case) |
| 6 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 9 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 12 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 18 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 24 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 30 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 36 (3 years) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 48 (4 years) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 60 (5 years) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 120 (10 years) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Standard parametric models were fitted to the observed data. Results of the extrapolation analysis are presented in Table 12 for tebentafusp PCP and Table 13 for pembrolizumab.

**Table 12. TTD parametric models and KM curve for tebentafusp pre-choice pembrolizumab 04-April 2022 DCO**

| Months | KM April 2022 DC) | Exponential | Weibull | Lognormal | Log-logistic | Gompertz | Generalised gamma |
|---|---|---|---|---|---|---|---|
| **AIC** | | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **BIC** | | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Ranking based on AIC and BIC** | | 3 | 5 | 6 | 1 | 2 | 3 |
| 6 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 9 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 12 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 18 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 24 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 30 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 36 (3 years) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 48 (4 years) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 60 (5 years) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 120 (10 years) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Table 13. TTD parametric models and KM curve for pembrolizumab 04-April 2022 DCO**

| Months | KM April 2022 DC) | Exponential | Weibull | Lognormal | Log-logistic | Gompertz | Generalised gamma |
|---|---|---|---|---|---|---|---|
| **AIC** | | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **BIC** | | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Ranking based on AIC and BIC** | | 2 | 3 | 6 | 4 | 1 | 4 |
| 6 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 9 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 12 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 18 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 24 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 30 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 36 (3 years) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 48 (4 years) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 60 (5 years) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 120 (10 years) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

# Other Model updates

## *Treatment adherence*

Adherence for treatment with tebentafusp was set at 92% in the model base-case with a sensitivity analysis at 90% and 95%.

### Clinical data

Tebentafusp is administered weekly as an infusion. In study IMCgp100-202 (13 October 2020 DCO), [redacted] of the patients treated with tebentafusp had an interruption at any time, with a mean duration of [redacted] days, and [redacted] had a reduction from protocol dose level.

Based on an analysis of dose interruption on the safety and efficacy of tebentafusp, after reaching 68 mcg, patients receiving tebentafusp can have one or two omissions of less than 2 weeks duration with minimal impact on safety and efficacy [2] (see Appendix L: Tebentafusp treatment adherence). That means up to four weeks a year or a compliance of 92% (48/52). The majority of treatment interruptions in the trial were [redacted]. Treatment restart was typically in the outpatient setting [redacted], without dose modification from most recent dose [redacted] or steroid premedication [redacted]. Grade 2 cytokine release syndrome (CRS) was uncommon at restart and occurred mostly in patients with preceding grade 2 CRS [2].

Based on Table 14, treatment interruption in the pembrolizumab arm was limited [redacted].

**Table 14. Dose interruptions and reductions – summary (Safety Analysis Set) IMCgp100 and pembrolizumab 13 October 2020 data cut-off**

| | | IMCgp100 (N=245) | Pembrolizumab (N=91) |
|---|---|---|---|
| Received intrapatient dose escalation as planned: | Yes | [redacted] | [redacted] |
| | No | | |
| No interruption and no reduction at any time | | [redacted] | [redacted] |
| At least one interruption or reduction | | | |
| No interruption at any time | | [redacted] | [redacted] |
| Number of patients with an interruption | Any | [redacted] | [redacted] |
| | 1 interruption | | |
| | 2 interruptions | | |
| | 3 interruptions | | |
| | 4 interruptions | | |
| | 5 interruptions | | |
| | 6 interruptions | | |
| | 7 interruptions | | |
| | 8 interruptions | | |
| | 9 interruptions | | |
| | 10 interruptions | | |
| | 12 interruptions | | |
| Total number of interruptions [1] | | [redacted] | [redacted] |
| Reason for interruption at any time | Missed Visit | [redacted] | [redacted] |
| | Adverse Event | | |
| | Delayed Administration | | |

| | | IMCgp100 (N=245) | Pembrolizumab (N=91) |
|---|---|---|---|
| | Other | [redacted] | [redacted] |
| | Scheduled visit not done | | |
| | Unknown | | |
| | Missing | | |
| Duration of interruption (days) | n | [redacted] | [redacted] |
| | Mean (SD) | | |
| | Median | | |
| | Min, Max | | |
| No reduction at any time | | [redacted] | [redacted] |
| At least one reduction | | | |
| Number of patients with a reduction from protocol dose level | Any | [redacted] | [redacted] |
| Number of patients with a reduction from protocol dose level | | | |
| | 1 reduction | [redacted] | [redacted] |
| | 2 reductions | | |
| | 4 reductions | | |
| Reason for reduction from protocol dose level | Adverse Event | [redacted] | [redacted] |
| | Other | | |

Interruptions are only counted if study drug administration restarts following interruption.
[1] The total number of interruptions is the sum of all patients' interruptions. It is the denominator of the reason for interruption at any time.
Source: Listing 16.2.5,- Output: t-14-03-01-00-02b-ex-dose02.

Program: t03010ex0dose02.sas Cutoff Date: 13OCT2020 04AUG2022 03:34

**Modelling approach**

Duration of treatment based on the date of first dose to date of discontinuation (i.e., time-to-discontinuation, TTD) does not account for missed doses or interruptions. A compliance of less than 100% reflects the interruptions seen in study IMCgp100-202 (Table 14). A compliance of 92% for tebentafusp reflects up to four doses missed in a year (two interruptions of up to two weeks, 48/52 weeks). The total combined costs of tebentafusp plus administration are weighted to account for the number of interruptions / missed doses for a compliance of 92%. Sensitivity analyses for compliance of 90% and 95% are also presented in the results section (Table 24).

An adjustment for adherence was not applied to pembrolizumab because the interval between infusion is 6 weeks and the burden on patients significantly less as demonstrated by the limited treatment interruptions in the trial (Table 14) and based on the extensive experience with pembrolizumab in a range of cancers.

### *Proportion of usage of the IC regimens*

Consistent with NICE's recommendation, cost-effective modelling was based on comparison of tebentafusp with pembrolizumab. Hence, the proportion of patients on pembrolizumab was set to 100% and 0% for the other two regimens in the IC arm, dacarbazine and ipilimumab.

**Table 15. Proportion of usage of the different regimens in the IC arm**

| **Investigator's choice** | **Prior** | **Updated (Addendum 1 25-APR-2022)** | **Update (Addendum 2 30-SEP-2022)** |
|---|---|---|---|
| **% on pembrolizumab** | 81.7% | 87.3% | 100% |
| **% on ipilimumab** | 12.7% | 12.7% | 0% |
| **% on dacarbazine** | 5.6% | 0.0% | 0% |

### *Tebentafusp stopping rule*

As recommended in the ACD, the 24-month stopping rule for tebentafusp was removed.

### *Other economic modelling parameters*

Remaining parameters were retained unchanged from the updated company case of Addendum 1 submitted on 25 April 2022. No changes were made to:

- IC treatment duration (modelling approach)
- Subsequent therapies
- Cost of chemo-therapy administration

Details of the changes made in Addendum 1, to the company base-case for the above parameters, are presented in Appendix M: model updates from Addendum 1 (25 April 2022) retained in Addendum 2.

## B.3 Cost effectiveness

### *B.3.7 Base-case results*

Base-case results of the economic analysis for a 38-year time horizon and with a discount rate of 3.5% for both costs and outcomes, are presented in Table 15.

In the updated Company base case model, tebentafusp provides a LY gain of [redacted] years ([redacted] vs. [redacted]), and a QALY gain of [redacted] QALYs ([redacted]). Both the improvement in life expectancy and in HRQoL of patients with metastatic UM is considered substantial. This improvement in modelled outcomes for patients with metastatic UM is driven mainly by the proportion of patients experiencing longer survival compared with the comparator and is consistent with the published results of study IMCgp100-202, which demonstrated a significant improvement in survival with tebentafusp versus investigator's choice.

Applying the PAS vial price of [redacted] for tebentafusp, the deterministic incremental cost-effectiveness ration (ICER) for the Company base-case was [redacted] per QALY (Table 8) and the probabilistic sensitivity analysis (PSA) ICER was [redacted] per QALY (Table 9).

**Table 16. Base-case results**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£/LYG) | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|---|
| Tebentafusp | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Comparator | [redacted] | [redacted] | [redacted] | NA | NA | NA | NA | NA |
| Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years | | | | | | | | |

### *B.3.8 Sensitivity analyses*

**Probabilistic sensitivity analysis**

A probabilistic sensitivity analysis (PSA) was conducted to describe how uncertainty around input parameters is translated into uncertainty around the estimated outputs of the model. Hence, suitable probability distributions were assigned to model parameters to characterise uncertainty around their mean values and have been presented in section B3 of the company submission (November 2021). Values were sampled from the corresponding parameter distributions and were assigned to each parameter in an iterative process. This process was repeated for 5,000 times, and the results of each of these iterations were used to determine the distribution of incremental costs and incremental QALYs.

When available, the mean value and the standard error of each parameter were used to parameterise the relevant probability distribution. When the latter was not available probability parameters were parameterised based on a 25% or 10% variation in the point estimate of the parameter.

The results of the PSA were presented within the cost-effectiveness plane in the form of a joint distribution of costs and QALYs, along with a mean value of the ICER and a 95% confidence interval ellipse (Figure 12). It is apparent that the largest spread is across the x axis of the scatter plot, showing that the highest uncertainty is associated with the health benefits. The probability that each treatment is cost-effective, resulting in the highest net monetary benefit, is presented over different values of a cost-effectiveness threshold in the form of a cost-effectiveness acceptability curve (CEAC) in Figure 13.

Table 17 presents the mean incremental costs and QALYs as well as the ICER as estimated in the base-case PSA.

**Table 17. Results of the base-case PSA**

| Technologies | Incremental cost (£) | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|
| Tebentafusp PCP | [redacted] | [redacted] | [redacted] |
| Pembrolizumab | - | - | - |
| **Abbreviations:** ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years | | | |

**Figure 12. Cost-effectiveness plane – incremental costs vs. incremental QALYs**

[redacted]

**Figure 13. Cost-effectiveness acceptability curve for willingness-to-pay threshold**

**Deterministic sensitivity analysis**

A univariate sensitivity analysis was conducted to establish those parameters with the greatest impact on the model's results. To determine the parameters to which the model was most sensitive, the model was evaluated with each parameter set at a lower and upper value while other parameters remained constant.

Upper and lower values of model parameters were determined by their 95% CIs or ±1.96 standard errors, depending on format of source data reporting. When no information was available regarding a parameter's uncertainty then the variation around the mean value was modelled by varying the parameter by 25% or 10% of its mean value.

A tornado diagram for the 10 parameters that produce the greatest variation on the ICER is shown in Figure 14 and the corresponding ICERs for the upper and lower estimates for each parameter are shown in Table 18.

Patient age at start of treatment produces the largest variation and is likely linked to the available lifetime over which patients may derive benefit. Utility at baseline produces the second highest variation in the ICER because it is linked to the utility of

patients surviving to one year before death from which a utility decrement is applied. Remaining parameters produce minimal variation in the ICER.

**Figure 14. Tornado diagram**

**Table 18. Results of the univariate sensitivity analysis**

| Parameter | ICER at lower value of parameter | ICER at upper value of parameter |
|---|---|---|
| Age (46.50, 77.50) | [redacted] | [redacted] |
| Utility Pre-progression IMCgp100-202 (0.76, 0.93) | [redacted] | [redacted] |
| Chemo subsequent attendance (123.75, 206.25) | [redacted] | [redacted] |
| Health states costs Pre-progression - cost per cycle (96.77, 161.28) | [redacted] | [redacted] |
| Proportion female (0.37, 0.62) | [redacted] | [redacted] |
| Overnight hospital stay (338.11, 563.51) | [redacted] | [redacted] |
| Adverse events disutility Treatment effect of dacarbazine (0.02, 0.03) | [redacted] | [redacted] |
| Adverse events disutility Treatment effect of tebentafusp (0.02, 0.02) | [redacted] | [redacted] |
| HLA screen (122.38, 203.97) | [redacted] | [redacted] |
| Data from the literature Time to death in days ≥360 days (0.74, 0.90) | [redacted] | [redacted] |

**Scenario analysis**

The impact of choice of parameter values were further explored through a number of scenario analyses. The scenarios that were evaluated are outlined below.

***Choice of method of extrapolation of PFS***

No changes were made to the modelling approach for PFS. Modelling was applied to the populations of interest, i.e., tebentafusp PCP subgroup versus pembrolizumab. As highlighted in Addendum 1 and demonstrated in Table 19, the scenario analyses for PFS produced minimal impact on the ICER.

**Table 19. Results of scenario analyses of alternative methods of extrapolating PFS**

| Scenario | ICER (£/QALY) | % change |
|---|---|---|
| Base-case KM + Generalised gamma | [redacted] | NA |
| KM + log-logistic | [redacted] | [redacted] |
| KM + log-normal | [redacted] | [redacted] |
| Generalised gamma | [redacted] | [redacted] |
| Log-logistic | [redacted] | [redacted] |
| Log-normal | [redacted] | [redacted] |
| Base-case (KM + generalised gamma; 10% at risk) | [redacted] | [redacted] |

***Choice of method of extrapolation of TTD***

We explored the choice of the method for the extrapolation of the TTD. Consistent with prior modelling (Addendum 1, April 2022) and conclusions of the NICE ACD, scenario analyses showed that plausible difference in TTD modelling had little impact on the cost-effectiveness results (Table 20).

**Table 20. Results of scenario analyses of alternative methods of extrapolating TTD**

| Scenario | ICER (£/QALY) | % change |
|---|---|---|
| Base-case KM + Exponential (25% for tebe; 15% pembro) | [redacted] | NA |
| KM + Generalised gamma (25% for tebe; 15% pembro) | [redacted] | [redacted] |
| Exponential (25% for tebe; 15% pembro) | [redacted] | [redacted] |
| Generalised gamma (25% for tebe; 15% pembro) | [redacted] | [redacted] |
| Base-case (KM + Exponential; both arms 10% at risk) | [redacted] | [redacted] |
| Base-case (KM + Exponential; both arms 15% at risk) | [redacted] | [redacted] |
| Base-case (KM + Exponential; both arms 25% at risk) | [redacted] | [redacted] |

***Source of utility data***

Since NICE concluded that "*the choice for estimating utility values is unlikely to be a driver of the cost-effectiveness results*", no changes were made to how utility data were modelled.

***Choice of method of extrapolation of overall survival***

As highlighted in the NICE ACD, OS modelling was highly uncertain and the incremental LYs and QALYs are driven by survival modelling for tebentafusp. To reduce the uncertainty and improve modelling of survival over the time-horizon beyond the observed data, the company has provided analyses based on longer follow up for survival, specifically the most recent data cut (04-April 2022) for study IMCgp100-202. In addition to survival modelling in the base case, the impact of alternative parametric models of OS for tebentafusp PCP on the ICER were tested. For the pembrolizumab group, the Weibull model was retained in the base case because it provided a clinically plausible estimation of survival beyond the observed data, which was consistent with the historical data of first-line treatments reported in the meta-analysis by Rantala et al [4].

The following alternative combinations of modelling OS for tebentafusp were tested, and results reported below (Tables 20-22):

- parametric models applied to the piecewise approach from [redacted] months (base case) (Table 21)
- parametric modelling from [redacted] months and [redacted] months using the piecewise approach (Table 22)
- standard parametric modelling of complete OS data (ITT) (
- Results of scenario analyses using parametric models in the tebentafusp PCP arm are presented in Table 23 for completeness. The fitted models overlaid with the KM plots are presented in Figure 15. The ICERs are significantly larger than the company base case. The company believes that standard parametric models do not appropriately capture survival in the tebentafusp arm as detailed in section Overall Survival, as the shape of the hazard of standard parametric models (Weibull, exponential, log-logistic, log-normal, Gompertz and generalised gamma) do not match that of tebentafusp (Figure 7). Indeed, as detailed in NICE TSD 14 on survival analysis [7], the exponential distribution has a constant hazard, and the Weibull and Gompertz are monotonically increasing or decreasing but cannot change direction. Therefore, these models could not capture the biphasic hazards in the tebentafusp arm. The log-normal, log-logistic and generalised gamma may have non-monotonic hazard, first with an increasing hazard and then a decreasing hazard, however the shape of the hazard of tebentafusp is distinct to that of these models. The graphs presented in Figure 15 show that the standard parametric models do not fit the tail of the observed data, contrarily to the piecewise models presented in Figure 8. The models do not capture the long-terms survivors and under-estimate the survival benefit of tebentafusp thus increasing the ICER.
- Table 23)

Results of the two models preferred by the ERG are shown below in Table 26.

With exception of the exponential model, all models produced ICERs of similar magnitude of change (plus or minus) around the ICER for the base case (Table 21) with a range of [redacted]. The piecewise log-normal model provides a mid-range estimate. The exponential model does not capture the proportion of long-term survivors and does not fit the tail of the KM curve, hence produced a much higher ICER because it does not capture the value of the long-term survivors.

**Table 21. Results of scenario analyses using alternative parametric survival models applied to piecewise approach**

| Scenario | ICER (£/QALY) | % change |
|---|---|---|
| **Base-case (APR2022 DCO)**<br>Piecewise-28, log-normal (tebentafusp PCP)<br>Weibull (pembrolizumab) | [redacted] | **NA** |
| Piecewise-28, Log-logistic (tebentafusp PCP)<br>Weibull (pembrolizumab) | [redacted] | [redacted] |
| Piecewise-28, Gompertz (tebentafusp PCP)<br>Weibull (pembrolizumab) | [redacted] | [redacted] |
| Piecewise-28, Gen Gamma (tebentafusp PCP)<br>Weibull (pembrolizumab) | [redacted] | [redacted] |
| Piecewise-28, exponential (tebentafusp PCP)<br>Weibull (pembrolizumab) | [redacted] | [redacted] |
| Piecewise-28, Weibull (tebentafusp PCP)<br>Weibull (pembrolizumab) | [redacted] | [redacted] |

Parametric modelling from 26 months and 27 months using the piecewise approach (Table 22) produced a range of ICERs between [redacted] per QALY.

**Table 22. Results of scenario analyses using alternative time points applied to piecewise approach for modelling survival**

| Scenario | ICER (£/QALY) | % change |
|---|---|---|
| **Base-case (APR2022 DCO)**<br>Piecewise-28, log-normal (tebentafusp PCP)<br>Weibull (pembrolizumab) | [redacted] | **NA** |
| Piecewise-26, log-normal (tebentafusp PCP) | [redacted] | [redacted] |

| | | |
|---|---|---|
| Weibull (pembrolizumab) | | |
| Piecewise-27, log-normal (tebentafusp PCP)<br>Weibull (pembrolizumab) | [redacted] | [redacted] |

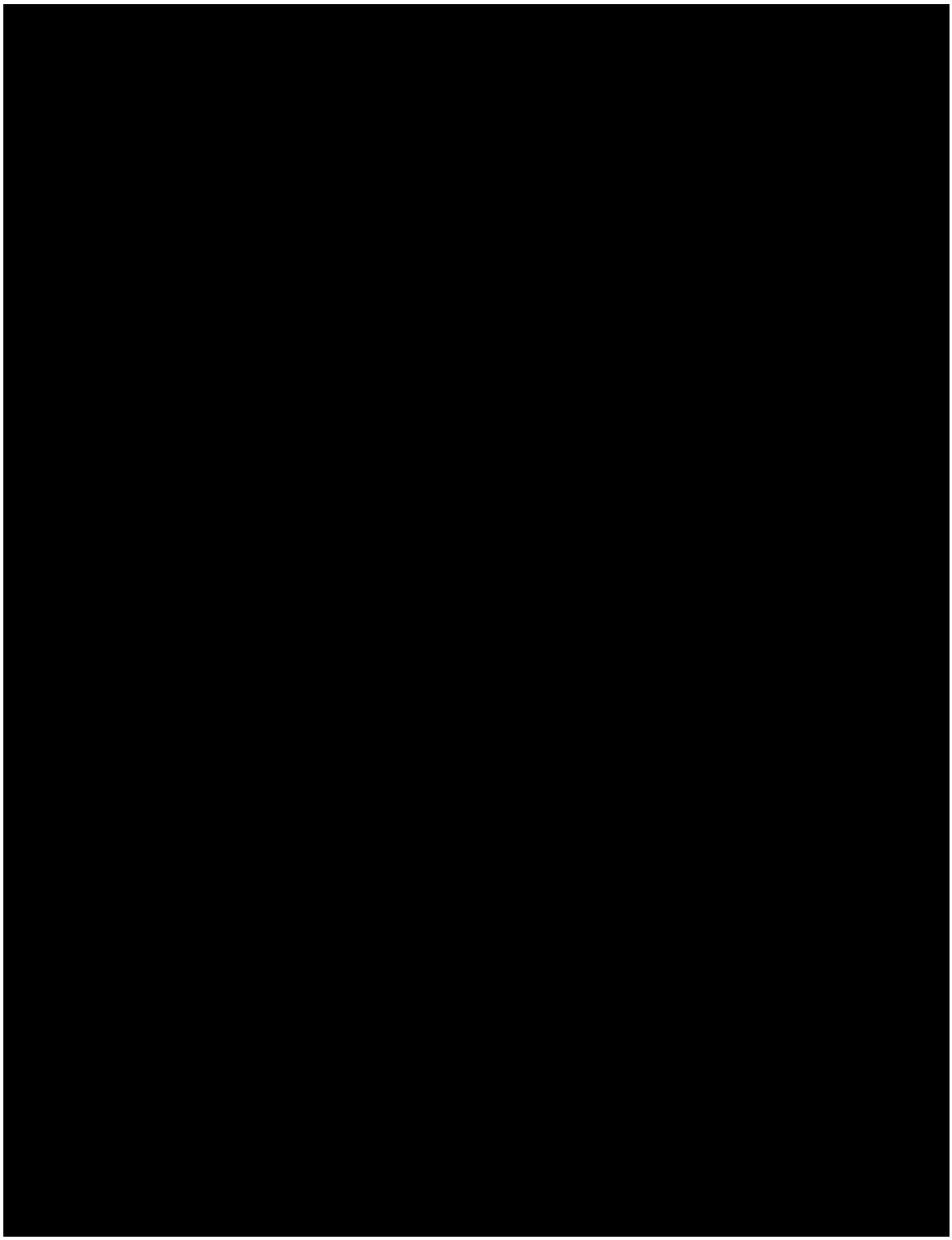
Results of scenario analyses using parametric models in the tebentafusp PCP arm are presented in Table 23 for completeness. The fitted models overlaid with the KM plots are presented in Figure 15. The ICERs are significantly larger than the company base case. The company believes that standard parametric models do not appropriately capture survival in the tebentafusp arm as detailed in section Overall Survival, as the shape of the hazard of standard parametric models (Weibull, exponential, log-logistic, log-normal, Gompertz and generalised gamma) do not match that of tebentafusp (Figure 7). Indeed, as detailed in NICE TSD 14 on survival analysis [7], the exponential distribution has a constant hazard, and the Weibull and Gompertz are monotonically increasing or decreasing but cannot change direction. Therefore, these models could not capture the biphasic hazards in the tebentafusp arm. The log-normal, log-logistic and generalised gamma may have non-monotonic hazard, first with an increasing hazard and then a decreasing hazard, however the shape of the hazard of tebentafusp is distinct to that of these models. The graphs presented in Figure 15 show that the standard parametric models do not fit the tail of the observed data, contrarily to the piecewise models presented in Figure 8. The models do not capture the long-terms survivors and under-estimate the survival benefit of tebentafusp thus increasing the ICER.

**Table 23. Results of scenario analyses using alternative parametric models applied to full survival data set**

| **Scenario** | **ICER (£/QALY)** | **% change** |
|---|---|---|
| **Base-case (APR2022 DCO)**<br>Piecewise-28, log-normal (tebentafusp PCP)<br>Weibull (pembrolizumab) | [redacted] | **NA** |
| Log-normal (tebentafusp PCP)<br>Weibull (pembrolizumab) | [redacted] | [redacted] |
| Log-logistic (tebentafusp PCP)<br>Weibull (pembrolizumab) | [redacted] | [redacted] |

| | | |
|---|---|---|
| Gompertz (tebentafusp PCP)<br>Weibull (pembrolizumab) | [redacted] | [redacted] |
| Gen. Gamma (tebentafusp PCP)<br>Weibull (pembrolizumab) | [redacted] | [redacted] |
| Exponential (tebentafusp PCP)<br>Weibull (pembrolizumab) | [redacted] | [redacted] |
| Weibull (tebentafusp PCP)<br>Weibull (pembrolizumab) | [redacted] | [redacted] |

**Figure 15. Overlay of KM plots and parametric models tebentafusp PCP and pembrolizumab 04 April 2022 DCO**



***Adherence***

A compliance of 92% is applied in the base-case to reflect the interruptions seen in study IMCgp100-202. Scenario analyses for 90% and 95% compliance are presented in Table 24. Neither scenario produced a significant effect on the ICER. The compliance rate is applied in the tebentafusp PCP arm only, as interruption in the pembrolizumab arm were very limited (Table 14).

**Table 24. Results of scenario analysis on compliance**

| Scenario | ICER (£/QALY) | % change |
|---|---|---|
| Base-case (92% compliance) | [redacted] | NA |
| 90% compliance | [redacted] | [redacted] |
| 95% compliance | [redacted] | [redacted] |

**Subgroup analysis**

The analysis of the survival endpoints for the pembrolizumab subgroup of the IC arm was not adjusted for cross-over because:

- There were too few patients (n=[redacted]) who crossed over to tebentafusp to adjust for differences between patients who crossed over and those that did not.
- Cross over was not mandated in the protocol so there was no clinical rule for determining the time of cross over, which would have produced significant additional uncertainty in an adjustment for cross-over.

Out of the [redacted] patients who crossed over, [redacted] experienced an event (death) and [redacted] were censored in the 04-April 2022 DCO.

To illustrate the possible impact of adjustment for cross-over, we presented a subgroup analysis censoring patients at the point of cross-over. As all patients who crossed-over had progressed and discontinued the IC treatment at the time of cross-over, this adjustment only impacts analysis of OS. The results demonstrate that the impact of censoring is very limited (Table 25) and demonstrate that a statistical adjustment for cross-over would have produced a minor change to the ICER, which

would have likely been lower than the base case. The company base case, not censoring at cross-over, is a conservative estimate.

**Table 25 Results of a subgroup analysis comparing pembrolizumab censored at cross-over to tebentafusp pre-choice pembro**

| Scenario | ICER (£/QALY) | % change |
|---|---|---|
| Base-case | [redacted] | NA |
| Subgroup – pembrolizumab censored at cross-over | [redacted] | [redacted] |

**Summary of sensitivity analyses results**

Since the main source of uncertainty highlighted by NICE was modelling of OS, sensitivity analyses focussed on modelling of survival with a secondary priority being treatment duration. Prior analyses demonstrated that modelling of PFS did not impact the cost-effectiveness results.

When compared with the pembrolizumab subgroup of the IC arm, the ICER for the tebentafusp subgroup pre-selected to receive pembrolizumab (PCP) is most sensitive to modelling OS of tebentafusp group, which is the major contributor to the calculation of incremental QALYs and produces a range of ICERs between [redacted] for the piecewise models that are most clinically plausible. Results from the PSA also demonstrates that there is significant uncertainty in the ICER associated with modelling survival in the base-case. This uncertainty is likely driven by the low number of patients at risk at the tail of the KM plots and is further underlined by results of the deterministic sensitivity analysis in which age, and thereby remaining life-expectancy at the start of treatment, produced the largest variation in the ICER.

The incremental costs are driven by the acquisition cost of tebentafusp, including IV administration costs, as shown in the disaggregated results Appendix J: Clinical outcomes and disaggregated results from the model.

**ERG preferred scenario**

The ERG preferred scenarios are presented for OS and time on treatment for tebentafusp PCP versus pembrolizumab, and results are reported in Table 26.

- OS – Log-logistic or generalised gamma applied to both arms for the complete dataset (i.e., not piecewise).
- Time of treatment – fully parametric generalised gamma for both treatments without adjustment for adherence for either treatment.

As detailed in Choice of method of extrapolation of overall survival, and presented in Figure 15, the standard parametric models do not fit the tail of the KM plot of tebentafusp. They do not capture the long-terms survivors, thus under-estimating the survival benefit of tebentafusp and increasing the ICER. Additionally, as detailed in section Extrapolation analysis Overall Survival, the hazard of the pembrolizumab and tebentafusp arm distinct (Figure 7), justifying using different modelling approaches and models in the two arms. The log-logistic and generalised gamma also over-estimate survival in the pembrolizumab arm, with a survival probability of 10% at 5-year compared to 3% based on historical data published by Rantala et al [4].

A stepwise implementation of the ERG preferred scenario is presented in Table 26, and demonstrates that the increase in the ICER is driven by then choice of OS in the tebentafusp arm.

**Table 26. Results of scenario analyses using ERG preferred scenarios**

| **Scenario** | **ICER (£/QALY)** | **% change** |
|---|---|---|
| **Base-case (APR2022 DCO)**<br>Piecewise-28, log-normal (tebentafusp PCP)<br>Weibull (pembrolizumab) | [redacted] | **NA** |
| Log-logistic (tebentafusp PCP)<br>Log-logistic (pembrolizumab) | [redacted] | [redacted] |
| Generalise gamma (tebentafusp PCP)<br>Generalise gamma (pembrolizumab) | [redacted] | [redacted] |
| Note: Time on treatment using generalised gamma applied to both arms | | |

**Table 27. Stepwise implementation of the ERG preferred scenario**

| Scenario | ICER (£/QALY) | % change |
|---|---|---|
| **Base-case (APR2022 DCO)**<br>Piecewise-28, log-normal (tebentafusp PCP)<br>Weibull (pembrolizumab) | [redacted] | **NA** |
| Change: TTD generalised gamma in both arms | [redacted] | [redacted] |
| Change: OS log-logistic in pembrolizumab arm | [redacted] | [redacted] |
| Change: OS log-logistic in tebentafusp PCP arm | [redacted] | [redacted] |
| Change: OS generalised gamma in pembrolizumab arm | [redacted] | [redacted] |
| Change: OS generalised gamma tebentafusp PCP | [redacted] | [redacted] |

## B.4 References


1. Immunocore, *Clinical Study Protocol IMCgp100-202*. 2018.
2. Max Schlaak, R.D., John M. Kirkwood, Anthony M. Joshua, Mohammed Milhem, Lauris Gastaud, Cornelia Mauch, Melinda Yushak, Sarah Lockwood, Conor Hayes, Alexander N. Shoushtari, *Safety and efficacy of infrequent tebentafusp treatment omissions in metastatic uveal melanoma patients* 2022.
3. Immunocore, *Clinical study report: IMCgp100-202*. 2021.
4. Rantala, E.S., M. Hernberg, and T.T. Kivelä, *Overall survival after treatment for metastatic uveal melanoma: a systematic review and meta-analysis.* Melanoma research, 2019. **29**(6): p. 561-568.
5. NICE-DSU, *NICE DSU TECHNICAL SUPPORT DOCUMENT 21: Flexible Methods for Survival Analysis.* 2020.
6. Office for National Statistics. *National Life Tables - life expectancy in the UK: 2018 to 2020*. 2021; Available from: https://www.gov.uk/government/statistics/national-life-tables-life-expectancy-in-the-uk-2018-to-2020.
7. NICE-DSU, *NICE DSU technical support document 14: survival analysis for economic evaluations Alongside clinical trials - extrapolation with Patient-level data.* 2013.

# B.5 Appendices

# Appendix J: Clinical outcomes and disaggregated results from the model

### Table 28. Summary of QALY gain by health state

| Health state | Tebentafusp | Comparator | Increment | Absolute increment | % absolute increment |
|---|---|---|---|---|---|
| Life years | | | | | |
| Pre-progression | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Post-progression | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| QALYs | | | | | |
| Pre-progression | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Post-progression | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Adverse events | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: QALY, quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

### Table 29. Summary of predicted resource use by category of cost

| Item | Tebentafusp | Comparator | Increment | Absolute increment | % absolute increment |
|---|---|---|---|---|---|
| Drug costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Administration costs | £9,595 | £1,207 | £8,388 | £8,388 | 695.1% |
| Subsequent therapy | £19,457 | £15,985 | £3,472 | £3,472 | 21.7% |
| Healthcare Resources - PFS | £5,877 | £3,456 | £2,420 | £2,420 | 70.0% |
| Healthcare Resources - PPS | £4,560 | £4,622 | -£62 | -£62 | -1.3% |
| Healthcare Resources - Death | £9,188 | £9,342 | -£154 | -£154 | -1.7% |
| AE | £168 | £368 | -£199 | -£199 | -54.2% |
| Total costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: Tech, technology; treat, treatment; admin, administration; mon, monitoring

# Appendix K: Checklist of confidential information

An updated confidential information checklist will be submitted as a separate document.

# Appendix L: Tebentafusp treatment adherence

**Pre-publication abstract for presentation at ESMO 2022**

**Authors:** Max Schlaak, Reinhard Dummer, John M. Kirkwood, Anthony M. Joshua, Mohammed Milhem, Lauris Gastaud, Cornelia Mauch, Melinda Yushak, Sarah Lockwood, Conor Hayes, Alexander N. Shoushtari

**Title**: Safety and efficacy of infrequent tebentafusp treatment omissions in patients with metastatic uveal melanoma

**Introduction**: Tebentafusp (tebe) (gp100×CD3) is the first TCR bispecific protein approved for treatment of a solid tumor (metastatic uveal melanoma, mUM). The IMCgp100-202 trial (NCT03070392) in untreated mUM demonstrated improved overall survival, HR=0.51.The most frequent treatment-related AEs (TRAEs), cytokine release syndrome (CRS) and rash, were consistent with mechanism of action and were most common in the first 3 weeks (wks). Once the target dose has been achieved after the first 3 intrapatient escalation doses, tebe is administered as outpatient. After the initial 3 wks, a subset of patients (pts) omitted at least one dose. Here, we assessed the impact on safety and efficacy of dose omissions that occurred beyond the initial 3 doses.

**Methods:** Planned dosing was 20 mcg (wk1), 30 mcg (wk2), and 68 mcg (wk3+). Omissions were required for certain AEs and also occurred for other elective reasons. Omissions beyond initial 3 wks were analyzed by reason, duration and safety (primarily CRS and rash) within 2 wks of restarting. CRS was evaluated per the ASCTC 2019 criteria. This analysis was conducted on the primary analysis (data cut-off 13Oct2020).

**Results:** 245 pts received tebe; median 23 doses. A total of 104 pts had omissions with 92/245 pts (38%) having an omission after the initial 3 wks. 56/92 pts (61%) had 1 omission; 14 pts had > 3 omissions. Most omissions were due to elective/other reasons (71%) or AEs (29%). 72% of omissions were ≤ 2 wks; 7% of omissions were > 3 wks.

Upon restarting, majority of pts did not have G3 TRAE (91%), G2 CRS (93%) or G2+ rash (93%) within 14 days. However, 6 pts had G2 CRS within 14 days of restart and all had prior G2 CRS.  1 or 2 omissions did not have a significant impact on OS when controlling for immortal time bias. The small numbers of pts with omissions > 3 wks duration limit the ability to evaluate impact on OS.

**Conclusions:** After reaching 68 mcg, patients receiving tebentafusp can have 1-2 omissions of ≤ 2 weeks duration with minimal impact on safety and efficacy. Treatment restart was typically outpatient (95%), without dose modification from most recent dose (98%) or steroid premedication (98%). G2 CRS was uncommon at restart, and occurred mostly in patients with preceding G2 CRS.

## Clinical data IMCgp100-202

### Table 30. Dose interruptions and reductions – summary (Safety Analysis Set)

| | | IMCgp100 (N=245) | Investigator's Choice (N=111) |
|---|---|---|---|
| Received intrapatient dose escalation as planned: | Yes | [redacted] | [redacted] |
| | No | | |
| No interruption and no reduction at any time | | [redacted] | [redacted] |
| At least one interruption or reduction | | | |
| No interruption at any time | | [redacted] | [redacted] |
| Number of patients with an interruption | Any | [redacted] | [redacted] |
| | 1 interruption | | |
| | 2 interruptions | | |
| | 3 interruptions | | |
| | 4 interruptions | | |
| | 5 interruptions | | |
| | 6 interruptions | | |
| | 7 interruptions | | |
| | 8 interruptions | | |
| | 9 interruptions | | |
| | 10 interruptions | | |
| | 12 interruptions | | |
| Total number of interruptions [1] | | [redacted] | [redacted] |

| | | IMCgp100 (N=245) | Investigator's Choice (N=111) |
|---|---|---|---|
| Reason for interruption at any time | Missed Visit | [redacted] | [redacted] |
| | Adverse Event | | |
| | Delayed Administration | | |
| | Other | | |
| | Scheduled visit not done | | |
| | Unknown | | |
| | Missing | | |
| Duration of interruption (days) | | | |
| | n | [redacted] | [redacted] |
| | Mean (SD) | | |
| | Median | | |
| | Min, Max | | |
| No reduction at any time | | [redacted] | [redacted] |

Interruptions are only counted if study drug administration restarts following interruption.
[1] The total number of interruptions is the sum of all patients' interruptions. It is the denominator of the reason for interruption at any time.
Source: Listing 16.2.5, Output: t-14-03-01-00-02-ex-dose.

Program: t03010ex0dose.sas Cutoff Date: 13OCT2020 05MAR2021 02:12

# Appendix M: model updates from Addendum 1 (25 April 2022) retained in Addendum 2 (30 September 2022)

## *Patient access scheme*

An updated PAS of [redacted] has been submitted to NHSE&I / PASLU and the model has been updated to reflect this new PAS. The list price of tebentafusp is [redacted] and [redacted] with PAS.

## *IC treatment duration*

The exponential distribution was applied instead of the generalized gamma, to align with the modelling approach taken in the tebentafusp arm.

## *Administration costs*

Administration costs were updated to align with the unit costs used in the budget assessment conducted by NHSE. The company adopted a single administration fee of £165 per infusion. The inpatient costs of the first 3 doses were captured within the costs of the overnight stay and hence the lower infusion cost of £165 per administration would avoid the risk of double-counting of extended infusions for the first cycle (i.e. 3 doses).

## *Subsequent therapies*

The proportion of usage of the different regimens following discontinuation of the primary treatment have been updated to align with clinical practice in the UK. According to clinical input during the NICE Decision Problem meeting (Monday 16th August 2021), ipilimumab+nivolumab combination therapy is rarely used, therefore, the proportion of patients receiving the treatment after either tebentafusp or the IC was reduced to 10%. The percentage of patients assumed to receive pembrolizumab after tebentafusp was adjusted accordingly. For the IC arm, since the vast majority (26%) of patients received pembrolizumab, the percentage of patients assumed to receive ipilimumab as the subsequent treatment was adjusted (Table 26).

**Table 31. Subsequent treatment usage**

| | Prior company case | | Updated company case | |
|---|---|---|---|---|
| | Tebentafusp | IC | Tebentafusp | IC |
| % of usage of ipilimumab + nivolumab | [redacted] | [redacted] | [redacted] | [redacted] |
| % of usage of ipilimumab (mono therapy) | [redacted] | [redacted] | [redacted] | [redacted] |
| % of usage of pembrolizumab | [redacted] | [redacted] | [redacted] | [redacted] |
| % of usage of nivolumab | [redacted] | [redacted] | [redacted] | [redacted] |
| **Total** | 100% | 100% | 100% | 100% |

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single technology appraisal

# NICE ID1441 IMCgp100-202 data update: November 2022

**(Academic in confidence, unpublished data)**

# Company evidence submission

**20th April 2023**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| **NICE_ID1441_IMCgp100-202 data sweep November 2022_redacted_180423** | **V 1** | **Yes** | **20th April 2023** |

Immunocore are committed to providing NICE with the latest data on tebentafusp to ensure decision making is informed by the most recent survival data. Clinical study IMCgp100-202 results for 3-year follow up will be available in July 2023, however a data cut was completed in November 2022, the results of which are presented below.

An updated data set of study IMCgp100-202 was obtained in November 2022. In Figure 1 the Kaplan-Meier curve for tebentafusp pre-choice pembrolizumab (PCP) and pembrolizumab is presented from November 2022. We note that the plateau in the tebentafusp PCP arm is maintained, further supporting that a proportion of patients experience long-term survival with tebentafusp. Additionally, we observed that the survival probability reaches 0 around five years in the pembrolizumab arm, in line with several studies [1, 2] and feedback from UK clinical experts.

**Figure 1. Kaplan Meier curve of overall survival for study IMCgp100-202 tebentafusp pre-choice pembrolizumab and pembrolizumab, November 2022 data cut-off**

Table 1 presents summary data on overall suvrival for tebentafusp PCP and pembrolizumab. Based on Figure 1 and the survival probabilities reported in

Table 1, it is expected that the 5-year survival probability in the tebentafup PCP arm will be around 20%, compared to 0% for currently available therapies based on several studies [1, 2] and feedback from UK clinical experts and the IMCgp100-202 control arm.

**Table 1. Summary of overall survival (pre choice pembrolizumab population) November 2022 data cut-off**

| | Tebentafusp PCP (N=199) | Pembrolizumab (N=103)* |
|---|---|---|
| Patients with deaths events | [redacted] | [redacted] |
| Median (95% CI), months | [redacted] | [redacted] |
| Survival probabilities (months) | | |
| 6 | [redacted] | [redacted] |
| 9 | [redacted] | [redacted] |
| 12 | [redacted] | [redacted] |
| 18 | [redacted] | [redacted] |
| 24 | [redacted] | [redacted] |
| 30 | [redacted] | [redacted] |
| 36 | [redacted] | [redacted] |
| 42 | [redacted] | [redacted] |
| 48 | [redacted] | [redacted] |
| 54 | [redacted] | |

***includes 14 patients who crossed over to the tebentafusp arm**

Figure 2 demonstrates that the fitted piecewise model (Kaplan-Meier curve plus log-normal extrapolation beyond 28 months) aligns with the observed data obtained in November 2022, supporting that the modelling approach used is appropriate. The data for the 3-year of survival follow-up will be available in July 2023 and the company can provided it as academic in confidence ahead of presentation at ESMO in October 2023. The 3-year follow-up will further reduce uncertainty in overall survival with tebentafusp and improve estimation of the percentage of patients who achieve longer-term survival benefit with tebentafusp.

**Figure 2. Overlay of Kaplan-Meier curves of overall survival for tebentafusp pre-choice pembrolizumab with the April 2022 (red curve) and November 2022 (blue curve) data cut-offs with the fitted piecewise model (KM+lognormal beyond 28 months) with the April 2022 data (black curve)**

References
1. Rantala, E.S., M. Hernberg, and T.T. Kivelä, *Overall survival after treatment for metastatic uveal melanoma: a systematic review and meta-analysis.* Melanoma research, 2019. **29**(6): p. 561-568.
2. Khoja, L., et al., *Meta-analysis in metastatic uveal melanoma to determine progression free and overall survival benchmarks: an international rare cancers initiative (IRCI) ocular melanoma study.* Ann Oncol, 2019. **30**(8): p. 1370-1380.

**Appendix 1**

Kaplan-Meier curves for overall survival in the intent to treat (ITT) analysis set comparing tebentafusp (IMCgp100) to Investigators choice (pembrolizumab, ipilimumab or dacarbazine), November 2022 read out from study IMCgp100-202

14 June 2023

IMMUNOCORE

Dear Vicky,

Thank you for engaging with the EAG to set up a meeting to resolve the model functionality issue they are experiencing.

Regarding the below request from the EAG (13th June 2023):

> *''The EAG have asked if the company model could be updated to reimplement the functionality previously implemented by the ERG associated with the inclusion of post progression health state costs that are not 'one-off'.*
> *They have asked if it would be possible to incorporate the ERG worksheet (that was previously implemented by the ERG) with associated functionality into the model. If this is not feasible, please could you prioritize implementing the post progression health state costs functionality (the ERG adopted monthly BSC costs per cycle in the post progression health state and removed the end of life costs)''*

The suggestion from the EAG to incorporate costs for Best Supportive Care (BSC) cumulatively for each cycle post-progression is contrary to the clinical advice that informed the company submission. Have the EAG consulted with clinicians to inform their request?

In the company model, BSC costs post-progression are accrued over the four months immediately prior to death and applied as an aggregate one-off cost, which is aligned with the published recommendation by McKendrick *et al.* 2016. The observed data from study IMCgp100-202 demonstrate a proportion of patients receiving tebentafusp experience unprecedented survival. Based on clinical feedback these patients do not require BSC for the duration of their remaining life after disease progression. Hence the suggestion from the EAG is contrary to the clinical experience and advice.

In addition to the costs for BSC, the company also included costs for subsequent treatments following discontinuation of tebentafusp or pembrolizumab (NICE preferred comparator). The options for subsequent treatments were aligned with what was used in patients in the randomised clinical trial IMCgp100-202. In the company model, the costs of these subsequent treatments were based on their average treatment duration and were applied as one-off costs after discontinuation of tebentafusp or pembrolizumab. The proportion for each subsequent treatment was also informed by UK clinical experts.

In the company model, post-progression costs were based on (i) subsequent treatment immediately after tebentafusp or pembrolizumab and (ii) a one-off cost for end of life Best Supportive Care. The company approach was validated with two leading UK clinicians with extensive experience of treating patients with metastatic uveal melanoma and experience with tebentafusp available in the early access program. We would be reassured to investigate such a significant change to the company model suggested by the EAG if they could kindly confirm the details of the clinical advice they have received from experts in metastatic uveal melanoma.

Kind regards,
[redacted]

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**Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma [ID1441]**

**Consultation on the appraisal consultation document – deadline for comments** 5pm on Tuesday 12 July 2022. Please submit via NICE Docs.

| | |
|---|---|
| | Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.<br><br>The Appraisal Committee is interested in receiving comments on the following:<br>• has all of the relevant evidence been taken into account?<br>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?<br>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?<br><br>NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:<br>• could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;<br>• could have any adverse impact on people with a particular disability or disabilities.<br><br>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced. |
| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | OcuMel UK |
| **Disclosure** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | None |
| **Name of commentator person completing form:** | [redacted], OcuMel UK |

| Comment number | Comments<br><br>Insert each comment in a new row. |
|---|---|

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**Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma [ID1441]**

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| | Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| Example 1 | We are concerned that this recommendation may imply that …….. |
| 1 | **Has all the relevant evidence been taken into account?**<br><u>Unmet need</u><br>We welcome the recognition of the severity of metastatic uveal melanoma and the acknowledgement that there is a burden on all uveal melanoma patients from regular scans and anxiety about developing metastases. This patient community are aware there are very limited treatment options.<br><br>Tebentafusp is a novel therapy and the first treatment that has shown a survival benefit for metastatic Uveal Melanoma patients. We are concerned that the recommendation does not fully recognise the unmet need of metastatic uveal melanoma patients who have no other treatment options.<br><br><u>Wider benefit</u><br>The wider benefit of Tebentafusp has also not been adequately considered. 50% of uveal melanoma patients will develop mets which have very few treatment options and a very poor prognosis.<br><br>All patients with uveal melanoma live with the prospect of developing metastatic disease.<br><br>All patients live with the anxiety of “watching and waiting” with regular testing for metastatic disease.<br><br>The extent to which these impact on patients’ Health Related Quality of Life and the real benefit of an effective treatment to even those patients who have not (yet) developed metastatic disease, has not been fully taken into account. |
| 2 | **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**<br><br>We note the committee’s concern with the modelling for overall survival and hope that Immunocore will submit data using the preferred approach which addresses the committee’s concerns and improve the overall clinical and cost effectiveness of Tebentafusp.<br><br>However, uncertainty about overall survival is common for new oncology treatments and we would consider that any clinical uncertainty could form the basis of a referral to the CDF rather than resulting in patients having no treatment options.<br><br>We do not consider the committee to have made reasonable interpretations of the evidence in regard to unmet need and the wider benefit of Tebentafusp (see earlier comments). |

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| | |
|---|---|
| 3 | **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**<br>Given our comments above, we do not agree that the recommendations are sound as they do not adequately reflect the burden of illness and the full benefits of Tebentafusp.<br>We agree that a two-year stopping rule would lack a clear clinical rationale and would not be appropriate to include in guidance to the NHS. Treatment should be made available to patients who are continuing to benefit from it beyond an arbitrary 2 year cut off. |
| 4 | |
| 5 | |
| 6 | |

Insert extra rows as needed

**Checklist for submitting comments**

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | [**Insert organisation name**] |
| **Disclosure** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | [**Insert disclosure here**] |
| **Name of commentator person completing form:** | Helen Evans, Patient Expert |

| **Comment number** | **Comments**<br><br>Insert each comment in a new row. |
|---|---|

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|---|---|
| Example 1 | We are concerned that this recommendation may imply that …….. |
| 1 | I agree with the submission made by OcuMel Uk by Jo Gumbs.<br>I particularly agree with the comments made in section 1, I am pleased to see that the committee has taken on board the severity of metastatic uveal melanoma and the effects on mental health of patients having uveal melanoma. I still do not think the committee have taken on board the fact that there is not one effective treatment available on the NHS to patients who go on to develop metastatic uveal melanoma. This is a huge worry and really must be taken into consideration. |
| 2 | 3.4 I am pleased to see that Tebentafusp has been recommended as first line treatment for metastatic uveal melanoma and can be used as second line treatment if required. |
| 3 | 3.10 Overall survival with tebentafusp<br>I think the committee has over stressed some of the uncertainty around modelling for overall survival and hopefully when Immunocore submit data in the preferred mode the committee can look at it more favourably. I feel like the whole overall effect of overstating any uncertainty has been to diminish the benefit that tebentafusp has most certainly offered to patients. This is a novel drug and patients I have spoken have most certainly benefitted from treatment. NICE want to see longer follow up of patients up to five years from start of treatment. This statement is exceptional if you look at the survival rates of untreated patients with metastatic uveal melanoma. It is a very aggressive disease and patients may only last a few months, or maybe up to 12 to 14 months if they are lucky. The prospect of living beyond two years, maybe up to five years would be a fantastic prospect for any stage four patient! I do not think the committee has grasped the very short time that some patients can survive without treatment. |
| 4 | 3.12 I am very pleased to see that the committee have concluded that it is not appropriate to stop treatment with tebentafusp after two years in patients who are responding well. |
| 5 | 3.14 Testing for HLA-A*02:01 Feedback from patients I have spoken to have said that this testing can take up to six weeks to get the results back thus delaying the start of treatment. Would it be possible to improve this delay at all? |
| 6 | 3.19 Tebentafusp has not been recommended for inclusion in the Cancer Drugs Fund<br>This is very disappointing. At what point will this be reviewed? The MHRA has approved tebentafusp for safety and efficacy but now the drug will only be available to those patients with sufficient health insurance or sufficient funds to self-fund treatment. This means that the only drug approved for use will be inaccessible to all but a very few patients. |
| 7 | Are the provisional recommendations sound and a suitable basis for guidance to the NHS?<br>No, I do not agree that the recommendation not to approve tebentafusp either for use on the NHS or the Cancer Drugs Fund is sound. The burden of illness to patients, the aggressive nature of the cancer and short life expectancy once diagnosed as stage 4 and the constant scanning of patients to check for metastatic growth has not been adequately considered in relation to the full benefits that this new drug can offer. There is more data to come, but in the mean time there is a clear benefit from treatment. |

Insert extra rows as needed

**Checklist for submitting comments**

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| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | [**Melanoma Focus**] |
| **Disclosure** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | [**None**] |
| **Name of commentator person completing form:** | **Dr Paul Nathan, Consultant Medical Oncologist, Mount Vernon Cancer Centre** |

| **Comment number** | **Comments**<br><br>Insert each comment in a new row. |
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|---|---|
| | The ACD decision reflects the committee's lack of confidence in the durability of benefit of treatment with tebentafusp. This is always a challenge when a new agent with a new mode of action is under appraisal.<br><br>We wish to draw the committee's attention to the following: |
| 1 | The case for a substantial improvement in survival for patients with metastatic uveal melanoma treated with tebentafusp has been proved and is accepted by the committee. Lack of access to the only treatment which improves survival for this area of high unmet clinical need would mean that:<br>a. Patients treated in the NHS would die sooner than they need to<br>b. Patients treated in the private sector would live longer than NHS patients<br>c. The standard of care of patients in the NHS would fall well below many other western healthcare economies. |
| 2 | We understand the company are providing additional data to the committee regarding longer term follow up of the phase I/II IMCgp100-102 patients. This may improve confidence in the durability of benefit experienced by some patients. We are also aware of many patients who remain on treatment after 2-3 years and are currently doing well.<br><br>Surely in a situation where clinical efficacy is proven but duration of benefit remains uncertain, the CDF would be an appropriate mechanism to allow access to patients of the only treatment that has been proved to improve survival for this disease whilst at the same time collecting data so that the durability of benefit can be assessed? |
| 3 | 1. It is not surprising that the shape of the KM curves for the tebentafusp and investigators choice populations are different. It is therefore reasonable to consider different models to best fit each curve. |
| 4 | |
| 5 | |
| 6 | |

Insert extra rows as needed

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# Comments on the ACD received from the public through the NICE Website

| | |
|---|---|
| **Name** | [redacted] |
| **Role** | |
| **Other role** | |
| **Organisation** | |
| **Location** | |
| **Conflict** | |
| **Notes** | |
| **Comments on the ACD:** | |

**Tebentafusp would be a welcome new treatment option**

**3.1 The patient experts explained that the addition of tebentafusp as a treatment option would bring significant hope to people with uveal melanoma,**

Comment:
Tebentafusp does indeed bring hope. Tebetafusp has seen me go from 9 tumours in my lungs to being in a position where resection was possible. This was not at the beginning as it was on both lungs. At the moment I have no visible cancer as of my last scan 11 weeks ago. I am 48 and have been living with metastatic disease for the last 3 years. My results on Tebe are something my specialist nurse has not seen in the last 8 years of working with metastatic ocular melanoma, although my oncologist says it is soon to get excited.

**There is no standard care for treating advanced uveal melanoma**

**3.2 The clinical experts explained that the treatments used are those licensed for melanoma (based on evidence for their clinical effectiveness in treating cutaneous melanoma), including pembrolizumab, nivolumab and ipilimumab immunotherapies, and dacarbazine chemotherapy. Most people with advanced uveal melanoma are offered pembrolizumab, some people are offered ipilimumab with or without nivolumab and a small minority who cannot take immunotherapies are offered dacarbazine.**

Comment:
Obviously, we are very grateful for these treatments and will need these as only around half of patients have the right HLA.

**Tebentafusp is a new drug with a novel mechanism of action**

**3.3 gp100, which is almost always found on the surface of uveal melanoma cells**

Comment:
As you have acknowledged there is no standard of care for ocular melanoma at the point of metastatic disease. However, it is my opinion that Tebentafusp should be standard of care for patients with the right HLA as it is targeted for our disease, hence the odds of it working increases.

**The IMCgp100-202 trial is generalisable to NHS practice for HLA-A*02:01-positive advanced uveal melanoma**

**3.5 The patient experts explained that some people are diagnosed with uveal melanoma in their 30s.**

Comment:
There were people in their 20's on the trial. Admittedly ocular melanoma is usually older people but I was diagnosed with my primaries in my early 30's and my secondaries in my mid 40's. Through involvement in the community I have met others my age and younger so I think it is unfair to see this disease as something that just affects older people. Many of us are still working age and indeed still work through our diagnosis

**3.5 They noted that tebentafusp is not suitable for some older people who might not be fit enough to have treatment. The committee also noted that it would only be suitable for people with HLA-A*02:01 (around 50% of the uveal melanoma population) as specified in the trial (see section 3.3).**

Comment:
This is exactly why it should be approved for those fit enough to use it. As ocular melanoma is a rare cancer it will be a small amount of people that need funding for this so although I would imagine it is very expensive it is a small group of people who will need unlike if it was a more common cancer.

**Tebentafusp improves overall survival and seems to have a benefit after disease progression but the reason for this is unclear**

**3.6 the median overall survival was longer in the tebentafusp arm (21.7 months) than in the investigator's choice arm (16.0 months).**

Comment:
When life span is so short 5.7 months is a very long time. It would make a huge difference to patients and their families

**Tebentafusp is associated with more adverse events than the usual treatments, but side effects are short in duration**

**3.8 The patient experts agreed that the adverse event profile of tebentafusp was better compared with other treatment options and that the adverse events that did occur were tolerable.**

Comment:
With a short life span the quality of life is very important and as noted the adverse reactions were more tolerable with Tebentafusp.

**It is not appropriate to include a 2-year stopping rule in the model**

**3.12 The committee concluded that it was not appropriate to include a stopping rule in the model because the clinical rationale for it had not been adequately justified.**

Comment:
As someone who has been taking Tebentafusp overt 2 years I appreciate this, as to stop a treatment that is working would be extremely stressful and seems unfair

**Tebentafusp is not recommended for routine use**

**3.18 So tebentafusp is not recommended for use in the NHS for treating advanced uveal melanoma.**

Comment:
I completely disagree with this decision and am really disappointed that ocular melanoma patients are being denied the most appropriate treatment for their disease. None of the drugs that have been proved most effective for our disease have been approved.

| | |
|---|---|
| **Name** | Rumana Hussain |
| **Role** | Clinical expert |
| **Other role** | |
| **Organisation** | |
| **Location** | |
| **Conflict** | |
| **Notes** | |

**Comments on the ACD:**

**Has all of the relevant evidence been taken into account?**

The evidence regarding cutaneous melanoma has been presented. Unfortunately there is little evidence on uveal melanoma due to the rarity of the condition

**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 race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?**

This is a very rare condition. As such the evidence submitted will never be as robust as a more common cancer. It therefore seems skewed to the disadvantage of these patients, especially when there is no alternative treatment available that gives tangible benefit.

Comment

Dear NICE committee
I am writing on behalf of all UK Ocular Oncology Teams to express the collective support for the approval of Tebentafusp for the treatment of metastatic uveal melanoma. Uveal melanoma is a rare ocular cancer with an incidence of approximately 650 cases in the UK per year, managed by four supra-regional highly specialised units. The treatments for local disease within the eye are successful; however, approximately 50% of patients develop metastatic disease. Progress in the treatment of metastatic disease has been minimal over many decades. Chemotherapy and immunotherapy have shown very little benefit in terms of disease control or prolongation of life so that metastatic is almost always fatal. The treatment of metastatic uveal melanoma is not standardised. Tebentafusp is the first systemic agent that has shown a significant benefit in a subgroup of patients with metastatic uveal melanoma. This is unmatched by any previous agents. We believe it to be groundbreaking in terms of its technological basis as well as patient outcomes. It gives our patients hope of treatment success

with unparalleled medium-to-long-term outcomes. There are presently no alternative treatments.
I hope you may consider this in your review of the NICE application for this drug. The opinion of the UK ocular oncology community is unanimously in support of its use.
Yours faithfully,
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## 1. Clinical effectiveness

### 1.1 Trial data available during original submission

The original trial (IMCgp100-202) was a randomised trial of 378 participants with metastatic uveal melanoma, comparing tebentafusp (n=252) to an active comparator treatment (n=126). Prior to randomisation, all 378 participants were assigned an Investigator's Choice (IC) of comparator treatment, which they would be given if they were later randomised to the comparator group. This meant that participants in the tebentafusp group were each in one of the IC categories, as follows: pembrolizumab: 199/252; ipilimumab: 40/252; dacarbazine, 13/252. Those randomised to the comparator group were given the comparator drugs as follows: pembrolizumab, n=103; ipilimumab, n=16; or dacarbazine, n=7.

At the October 2020 data cut off, OS favoured tebentafusp with a hazard ratio (HR) of 0.51 (95% confidence interval (CI) 0.37 to 0.71; P<0.0001). At a median follow-up duration of 11.4 months, median progression-free survival (PFS), assessed by investigator, was 3.3 months (95% CI 3.0 to 5.0) in the tebentafusp arm and 2.9 months (95% CI 2.9 to 3.0) in the IC arm (HR 0.73; 95% CI 0.58 to 0.94).

### 1.2 New data based on April 2022 cut-off

In the first addendum analysis, tebentafusp was required to be compared to pembrolizumab only. For optimal internal validity, it was deemed appropriate for only the 199 tebentafusp participants who had been assigned an IC of pembrolizumab to be compared to the randomised pembrolizumab participants. Table 1 demonstrates that the three groups defined by pre-randomisation IC were different in terms of baseline lactate dehydrogenase (LDH), size of largest metastatic lesion and size of largest liver lesion, which supports this strategy. Therefore, the addendum sample were: tebentafusp (n=199), pembrolizumab (n=103).

**Table 1. Summary of baseline disease characteristics by investigator pre-choice of therapy in Intent-to-Treat population 04 April 2022 data cut off**

| | Dacarbazine (N=20) | Ipilimumab (N=56) | Pembrolizumab (N=302) |
|---|---|---|---|
| **Baseline LDH** | | | |
| LDH ≤ ULN 250 U/L (n, %) | [redacted] | [redacted] | [redacted] |
| LDH > ULN 250 U/L (n, %) | [redacted] | [redacted] | [redacted] |
| n | [redacted] | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Min, Max | [redacted] | [redacted] | [redacted] |
| **Baseline Largest Metastatic Lesion** | | | |
| ≤ 3cm | [redacted] | [redacted] | [redacted] |
| 3.1-8.0 cm | [redacted] | [redacted] | [redacted] |
| ≥8.1 cm | [redacted] | [redacted] | [redacted] |
| n | [redacted] | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Min, Max | [redacted] | [redacted] | [redacted] |
| **Baseline Largest Liver Lesion** | | | |
| < 3 cm | [redacted] | [redacted] | [redacted] |
| ≥ 3 cm | [redacted] | [redacted] | [redacted] |
| No liver lesion | [redacted] | [redacted] | [redacted] |

| | Dacarbazine (N=20) | Ipilimumab (N=56) | Pembrolizumab (N=302) |
|---|---|---|---|
| n | [redacted] | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Min, Max | [redacted] | [redacted] | [redacted] |

**EAG comment:** The original randomisation of all 378 participants was stratified for LDH level, not pre-randomisation choice of comparator. Although there is likely to be a correlation between lactate dehydrogenase levels and the IC treatments, there may have been other criteria influencing investigator's choice, and so stratification for the investigator's choice cannot be said to have been carried out. This may have led to a small risk of a random imbalance in prognostic factors (associated with investigator's choice) across the two main groups. However, limiting the analysis to those with an IC designation of pembrolizumab, risk of selection bias from this source is eliminated. Despite the final sample of 302 participants (restricted to those with an IC designation of pembrolizumab) being only a sub-group of those originally randomised, the two groups [tebentafusp (n=199), pembrolizumab (n=103)] can still be regarded as properly randomised. This is because the randomness of each participant's allocation is independent; the removal of other participants with a different IC categorisation from both groups will not change this.

Fourteen participants crossed over from pembrolizumab to tebentafusp after the first interim analysis. The company considered 3 strategies for this:

1. censoring of those who crossed over,
2. exclusion of those who crossed over, and
3. a full intention-to-treat (ITT) approach, with no censoring or exclusion.

The company elected to use the full ITT approach for the base case: "*Hence, the model base case used the pembrolizumab subgroup, not censoring at cross-over to use all the OS data available for the pembrolizumab subgroup (i.e., including survival follow-up when patients had crossed-over from pembrolizumab to tebentafusp)*". The overall survival for death of tebentafusp v pembrolizumab favoured tebentafusp in all three approaches: [redacted] [full ITT approach], [redacted] [censored] and [redacted] [exclusion].

All patients crossing over had disease progression and so cross-over did not affect the PFS outcome (as all crossovers had therefore reached their endpoint). In any event, PFS data are not provided in the April (or November) data cut-offs, as data were regarded as mature by the company: number of events were [redacted] out of 256 patients for the tebentafusp ITT group and [redacted] out of 126 in the investigators' choice arm.

The third option, chosen by the company, is methodologically the most robust, as it mirrors the reality of clinical practice, and the former options (particularly exclusion) will tend to lead to a less conservative estimate of effect.

The lack of inclusion of PFS data in the addendum is explained by the existence of mature data, but it should be noted that it also allows the company to remove from active consideration an outcome that demonstrates less favourable results than overall survival (OS).

The company also had longer-term data from a single-arm tebentafusp study (IMCgp100-102). The figure below shows the single-arm data from this study at three separate data cut-offs.

**Figure 1. Study IMCgp100-102 Overall survival from the different data cut-offs - All particpants (N=146).**

### 1.3 Newest data based on November 2022 cut-off

Longer term data were available for the tebentafusp participants in the pembrolizumab IC category (n=199) and pembrolizumab participants (n=103) groups in November 2022 (Figure 2). The company noted that "*the plateau in the tebentafusp PCP arm is maintained, further supporting that a proportion of patients experience long-term survival with tebentafusp. Additionally, we observed that the survival probability reaches 0 around five years in the pembrolizumab arm.*"

**Figure 2. Kaplan Meier curve of overall survival for study IMCgp100-202 tebentafusp pre-choice pembrolizumab and pembrolizumab, November 2022 data cut-off**

The company also overlaid the April 2022 and November 2022 tebentafusp data, and extrapolated to 84 months and beyond based on this (Figure 3).

**Figure 3. Overlay of Kaplan-Meier curves of overall survival for tebentafusp pre-choice pembrolizumab with the April 2022 (red curve) and November 2022 (blue curve) data cut-offs with the fitted piecewise model (KM+lognormal beyond 28 months) with the April 2022 data (black curve)**

Based on these data, the company stated that "*the 5-year survival probability in the tebentafusp PCP arm will be around 20%, compared to 0% for currently available therapies*".

**EAG comment:**

- The company's assertion that survival will be zero by 5 years in the pembrolizumab group is based on a very large vertical drop in overall survival for the pembrolizumab group to zero, between 48 and 51 months. This initially appears unlikely, but the very low numbers at risk in the pembrolizumab group at that point explain this apparently implausible reduction. With only 2 at risk at 48 months, only 2 deaths are required to lead to a precipitous drop to zero cumulative survival.
- Although the point estimates in figure 2 appear to be correct, the lack of precision estimates around these data are a problem. The company appears to be quite certain in its statement that the pembrolizumab survival will be zero at 5 years in the overall population, but such certainty cannot be assumed. The EAG would like to see measures of uncertainty provided for the KM plots.
- There is also a large drop in the number at risk at around 60 months for the tebentafusp group, due to censoring. Because this is due to censoring, this does not, of course, reduce cumulative survival. However, the EAG would like to know the reasons for censoring of these people. It is possible that the reasons for censoring are completely non-informative, but they could also be associated with an increased risk of death. It cannot be assumed that these people would have remained alive.
- Following on from the above point, the extrapolated (84 months) overall survival for tebentafusp (Figure 3) appears to have an uncertain basis, given the very large numbers of censored participants after 48 weeks in both the April and November cut-offs. In addition the data from the long-term one arm tebentafusp study (Figure 1), where the point estimate of overall survival appears to be around 10-12%, do not agree with the notion that tebentafusp survivability would be as high as 20% in the long-term.
- Overall, there is a large lack of certainty in the company's statement that there would be a 20% survival on tebentafusp and a zero percent survival on pembrolizumab.

## 2. Cost-effectiveness

### 2.1 Summary of company's changes compared with the original CS

Compared with the original CS, CS addendum 1 did include updates for:

- Tebentafusp overall survival (OS)
  - Updated data cut (February 2022 ITT)
  - Assumed a 3-knot spline distribution
- Time to treatment discontinuation (TTD)
  - Assuming a piecewise model (Kaplan-Meier + exponential distribution for extrapolation) with different cut-off points (25% and 15%) for tebentafusp and the comparator respectively.
- Tebentafusp treatment costs
  - Updated tebentafusp PAS [redacted]. The list price of tebentafusp is [redacted] and [redacted] with PAS.
  - Removal of tebentafusp 18-month cap on the treatment costs
  - Introducing a 24-month tebentafusp stopping rule
  - Assuming 95% (instead of 100%) compliance to reflect approximately two 1 week breaks per year
  - Cost of administration
- Investigator's choice (IC) treatment costs
  - Proportion of usage of the different regimens (pembrolizumab, ipilimumab and dacarbazine) in the IC arm (CS addendum Table 2)
  - Cost of administration
- Subsequent treatment costs
  - The proportion of subsequent treatment with ipilimumab+nivolumab combination therapy was reduced to 10% for both tebentafusp and IC
  - The proportion of subsequent treatment with ipilimumab monotherapy was reduced to xxx for tebentafusp only, this was increased to [redacted] for IC
  - The proportion of subsequent treatment with nivolumab monotherapy was reduced to xxx for tebentafusp only (this was xx for IC, as in the CS base-case)
  - The proportion of subsequent treatment with pembrolizumab was increased to xxx for tebentafusp only (this was xxx for IC, as in the CS base-case)

Compared with the CS addendum 1, CS addendum 2 did include updates for:

- Population
  - The population was restricted to patients that were pre-selected to receive pembrolizumab prior to randomisation, termed "pre-choice pembrolizumab" (PCP) subgroup (for both tebentafusp and the comparator).
- OS
  - Updated data cut (April 2022 PCP)
  - Assuming piecewise model for tebentafusp (Kaplan-Meier + log-normal distribution for extrapolation; cut-off point: xx xxxxxx).
  - Assuming a Weibull distribution for IC (consistent with the original CS)
- PFS (approach consistent with original CS)
  - Original CS data cut (August 2021 ITT)

    - Assuming piecewise model for both tebentafusp and the comparator (Kaplan-Meier + generalised gamma distribution for extrapolation; cut-off point: 15%).
- TTD
    - Updated data cut (April 2022 PCP)
    - Assuming a piecewise model (Kaplan-Meier + exponential distribution for extrapolation) with different cut-off points (25% and 15%) for tebentafusp and the comparator respectively.
- Tebentafusp treatment costs
    - Identical tebentafusp PAS as CS addendum 1
    - Removal of the 24-month tebentafusp stopping rule
    - Assuming 92% compliance

The estimated ICERs (probabilistic) for the CS base-case, CS addendum 1 and CS addendum 2 were xxxxxxxxx xxxxxxxx and xxxxxxx per QALY gained respectively. The original EAG base-case ICER range (based on the original CS) was xxxxxxxx xx xxxxxxxx per QALY gained.

### *2.2 EAG comments*

#### 2.2.1 OS, PFS and TTD

CS addendum 2 does not provide a comprehensive assessment systematically considering the appropriateness of different (standard) approaches to estimate OS, PFS and TTD. Therefore, the EAG does not find compelling evidence to deviate from the original EAG preferences. Specifically, as described in section 4.2.6 of the original EAG report, a) the piecewise approach adopted by the company for OS, PFS and TTD, b) using Rantala et al. 2019 to verify OS extrapolations; c) assuming no treatment waning in the CS base-case and; d) consistency with the ACD.

a) The company adopted a piecewise approach to estimate OS, PFS and TTD. In general, the EAG does not prefer using KM curves (as done in the piecewise approach) for economic models as it might overfit the trial data which seems suboptimal for decision-making focussing on UK clinical practice. This might be specifically applicable to this case, given that the drop at 12 weeks was trial protocol-driven, which might not be representative for clinical practice. Moreover, NICE DSU TSD 21 on flexible methods for survival analysis highlights that the selected cut-point may be arbitrary and potentially importantly influence the results of an analysis. Potentially controversially, the cut-point in the current analyses was treatment dependent. In addition to the above, based on the company's response to clarification question C6a it became clear that the estimation and implementation of the piecewise models incorporated in the economic model deviates from common practice and the piecewise models described in NICE DSU TSD 21. The implemented piecewise models are using parametric survival models estimated from baseline (time = 0; using the full dataset) instead of being estimated specifically from the cut-point. This approach is flawed according to the EAG as these parametric survival models, estimated from baseline, are not intended to be used after the cut-point only as the proportion of patients surviving up to this cut-point (i.e. conditional survival) using these parametric survival models might differ from the conditional survival based on the KM curve. Given the aforementioned limitations of the company's piecewise approach, potentially controversial cut-points and flawed implementation by the company, the EAG prefers to use a standard parametric approach to estimate OS, PFS and TTD in its base-case.
b) For validating the extrapolations with external data, the company stated that the data reported by Rantala et al. 2019 on first-line patients is the best benchmark available for comparison

against the comparator. However, the company appreciated that these patients were treated with conventional chemotherapy, chemoimmunotherapy, hepatic intra-arterial chemotherapy and transarterial chemoembolization and treatment modality thus differs from the pembrolizumab arm of the IMCgp100-202 trial (PCP subgroup). Moreover, the EAG noted that this review potentially considered old studies (inclusion period 1980 to 2017) and most studies were retrospective analyses. Nevertheless, the EAG agrees that this is a useful benchmark (though it is unclear why the company digitised a plot from "Supplemental digital content 4" of the paper instead of from Figure 3 in the main manuscript). Given the above, the EAG believes this source should potentially be used as a 'lower limit benchmark' ruling out OS estimations of pembrolizumab that fall below the OS estimated based on these historic data. Especially for the first 3 years as after 3 years data only few patients are at risk, see Figure 3 in Rantala et al. 2019.

c) In the CS base-case no treatment waning was assumed, i.e. the PFS and OS were assumed to be different for tebentafusp and pembrolizumab for the whole duration of the time horizon. This was not appropriately justified in the CS. Given i) it is unclear whether assuming a continued treatment effect over the lifetime horizon of the model is plausible; ii) the uncertainty related to the long-term extrapolations (only xx xxx x patients were at risk at 36 months for tebentafusp and pembrolizumab respectively, while this is x xxxx at 48 months, see CS addendum 2 Figure 1) and; iii) the xxxxxxxx of QALY gains are accumulated beyond the observed data period (CS addendum 2 Table 8). For the latter it should be noted that it is unclear how the proportion of gains are exactly calculated (i.e. whether similar methods were applied as in Table 5.1 of the EAG report, based on clarification response C20). Alternative assumptions related to extrapolation treatment waning should be explored by the company.

d) According to the ACD "*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, indicating disease cure, as suggested by the company's approach*". The company's approach to estimate OS is, according to CS addendum 2 Figure 8, seemingly resulting in a plateau. In addition, the committee stated that: "*On balance using a standard parametric approach to extrapolate the data in both treatment arms was preferable*". Notably, the committee stated that for PFS and TTD: "*Either piecewise or fully parametric models are reasonable*" noting that "*the differences had little impact on the cost effectiveness results".* However, it was explicitly stated that the committee preferred "*using standard parametric curves for extrapolating overall survival*" while the company used piecewise models to estimate OS, PFS and TTD.

Given the above and consistent with the original EAG report, the EAG preferred using used the generalised gamma distribution and the log-logistic distribution (producing an ICER range) for OS and the generalised gamma distribution for both PFS and TTD (same distribution for bother treatments for all three outcomes).

### 2.2.2 Costs

The company updated the model following the recommendations from the EAG original report, NHSE, and the committee meeting by, for instance, removing the 18-month cap on the treatment cost, and not including a stopping rule after 24 months. However, CS addendum 2 did not provide new compelling evidence on some of the main issues presented in section 4.2.9 of the original EAG report. The main concerns of the EAG relate to: a) one-off application of BSC costs and b) unclear applicability to UK setting of subsequent therapies and population weight and height.

a. BSC costs were applied in the model as a one-off cost after the cohort left the PFS state at each cycle. The one-off costs were based on the study by McKendrick et al. 2016 in which BSC was provided for an average of four months (for both treatments). Hence, the one-off costs reflected the average BSC costs of 4 months, i.e. applied unrelated to the estimated time in the progressive disease (PD) health state. The company elaborated on the validity of the study of McKendrick and colleagues for the case of metastatic UM. However, the explanation on why the BSC costs were not applied per cycle in the PD health state was not considered appropriate by the EAG. Since post-progression costs would most likely depend on how long patients stayed in the PD state, this approach would benefit tebentafusp, as patient after tebentafusp stayed longer in the PD health state than for IC (see also Table 5.1). Despite requested by the EAG (clarification question C16), the company did not provide a scenario analysis (and updated economic model) applying monthly BSC costs per cycle in the PD health state. The company stated that would be inappropriate as it would lead to double-counting with end of life costs, as patients incurred end of life costs at the point of death. However, in the clarification question C15, the company stated that end of life costs had a limited impact on the incremental cost effectiveness ratio (ICER; difference less than £50). Therefore, the EAG would prefer to implement monthly BSC costs per cycle in the PD health state while removing end of life costs to prevent potential double counting (also given the minimal impact of end of life costs on the estimated ICER).
b. The EAG considered the estimation and applicability to UK practice to be uncertain for i) patients' weight and height, and ii) common subsequent therapies strategy.
    i. Pembrolizumab acquisition costs were determined by the patient's weight respectively. However, the company did not include the normal distribution for the UK population weight and height in their analyses (instead only the average patient weight and height are used). Incorporating these data would result in more accurate estimations of the average number of vials required per patient.
    ii. Subsequent therapies following discontinuation of the active treatment were accounted for in the economic model from data of the IMCgp100-202 trial. This potentially did not reflect the UK clinical practice. The company updated the subsequent treatment usage percentage in CS Addendum 1, according to the clinical input from the NICE Decision Problem meeting on Monday 16th August 2021 (see Section 2.1). However, the calculation, justification and thus plausibility of subsequent treatment percentages remains unclear. Moreover, the calculation of subsequent therapies duration remains unclear.

In addition, there are two main issues from CS Addendum 2, that the EAG would like to remark: a) missing adherence of pembrolizumab, b) updated administration costs, and c) applicability of subsequent therapies for patients initially treated with pembrolizumab.

a) The company included an option to incorporate adherence for treatment only for the tebentafusp arm (which was set at xxx at base-case), but not for pembrolizumab. The adherence parameter was set to affect the drug costs and administration costs (but not the subsequent therapy costs). The methods used to estimate this 92% were unclear to the EAG (based on Addendum 2 Appendix L the EAG could not reproduce this estimate). Scenario analyses on the adherence of tebentafusp had a slight impact on the ICER (between a decrease of 2.9% and increase of 4.4%). Additionally, no adherence correction was incorporated for pembrolizumab. Compelling evidence is missing on why the pembrolizumab adherence was not included, as compliance would be unlikely to be 100% in either arm. As per Table 14 of CS addendum 2, xxxxx xx xxxxxxxx x xxxxx xx xxx with pembrolizumab required a dose interruption, with a mean duration of xx days. Hence the EAG, would recommend including an adherence

correction for pembrolizumab (consistently as done for tebentafusp) or not implementing an adherence correction for both tebentafusp and pembrolizumab.

b) The company updated the unit cost for administration costs for first attendance and subsequent deliveries in both intervention and comparator to £165. According to the company only a single administration fee should included, as the inpatient costs would be included in the overnight stay (£450.81) and avoiding the risk of double-counting. However, this choice may underestimate the costs of the administration for both intervention and comparator. For the comparator (i.e., pembrolizumab), no overnight stay was stated to be necessary in the CS; thus, the initial health unit cost used in the original CS should be used (i.e., there would be no double-counting). For the intervention, as per CS, tebentafusp was assumed to be administered in the inpatient setting with an overnight monitoring for the first three doses, due to possible toxicity, and in a day case setting for the remaining doses. For the first 3 doses, there should be vital signs monitoring prior to the dose administration and every four hours for at least 16 hours after dosing. Therefore including only the administration fee per infusion seem to be underestimating the costs, even if including the overnight stay fee. Following the National Cost Collection data (2021/22), there are three options for delivering simple parenteral chemotherapy at first attendance (SB12Z), and for delivering subsequent elements of a chemotherapy cycle (SB15Z) (See Table 2.1). The company should have further justified the reduction of administration costs, as the hospital overnight stay may underestimate the costs incurred per patient during the first attendance. Moreover, as the subsequent attendance would not require overnight stay in neither intervention nor comparator; therefore, reducing the cost would unlikely reflect clinical reality. Hence, the EAG would prefer to use the costs described in the National Cost Collection data, i.e. consistent with the original CS.

c) Subsequent therapies following discontinuation of the active treatment were accounted for in the economic model and were updated in the CS Addendum 1. Given the change of pembrolizumab as the key comparator in CS Addendum 2, the EAG would like to see further justification on the percentage of usage of the different regimens following discontinuation of the primary treatment for the comparator arm (i.e., pembrolizumab), especially given that 42% of the subsequent immunotherapy consist of pembrolizumab. The EAG request an update of the subsequent treatment usage with the new key comparator accompanied with further clinical justification. This justification should also include why the estimated subsequent therapies are different for patients that initially received tebentafusp and pembrolizumab.

**Table 2.1: Administration cost as per National Cost Collection data (2021/22)**

| Currency code | Currency description | Service description | National Average Unit cost |
|---|---|---|---|
| SB12Z | Deliver Simple Parenteral Chemotherapy at First Attendance | Daycase and Reg Day/Night | £313.91 |
| SB12Z | Deliver Simple Parenteral Chemotherapy at First Attendance | Outpatient | £207.59 |
| SB12Z | Deliver Simple Parenteral Chemotherapy at First Attendance | Other | £188.06 |

| | | | |
|---|---|---|---|
| SB15Z | Deliver Subsequent Elements of a Chemotherapy Cycle | Daycase and Reg Day/Night | £383.54 |
| SB15Z | Deliver Subsequent Elements of a Chemotherapy Cycle | Outpatient | £326.46 |
| SB15Z | Deliver Subsequent Elements of a Chemotherapy Cycle | Other | £186.56 |

Given the above and consistent with the original EAG report, the EAG would prefer the company to: a) implement monthly BSC costs per cycle in the PD health state while removing end of life costs to prevent potential double counting (also given the minimal impact of end of life costs on the estimated ICER), b) further clarify the calculation of the duration of subsequent treatment and its applicability to the UK setting; c) include adherence consistently for both tebentafusp and pembrolizumab, d) update and modify administration costs (consistent with the original CS) and e) justify and potentially update the subsequent treatment percentages and duration.

### 2.2.3 Health-related quality of life

CS addendum 2 did not include new compelling evidence responding to the main concerns reported in section 4.2.8 of the EAG original report. More specifically: a) predominantly using TA366 utility values instead of IMCgp100-202 trial data; b) handling of EQ-5D IMCgp100-202 trial data and c) the time-to-death utility approach adopted by the company.

a) The CS base-case predominantly used utility values from TA366 instead of EQ-5D data from the IMCgp100-202 trial. This was justified by the company by stating a high proportion of missing EQ-5D data from the IMCgp100-202 trial, see Table 62 of the original CS. Thus, the CS base-case relied heavily on literature for obtaining utility values; however, the SLR performed by the company did not identify any relevant studies. The EAG considered that the justification on the use of utilities derived from TA366 (considering pembrolizumab in advanced melanoma not previously treated with ipilimumab) was insufficient, as the study focused on a different population with different treatment options. In addition, the company did not elaborate on the suitability of the data from other NICE appraisals that were used (such as TA319 and TA384) in terms of different populations and treatment. This is particularly relevant given the company stated that there are no NICE TAs relevant to this decision problem (clarification response C24). According to the company's response to the request for clarification, tebentafusp is the first treatment under evaluation by NICE for the treatment of metastatic UM. The company stated that UM is biologically distinct from skin melanoma with different physiological, genetic, and epidemiologic characteristics. According to the EAG, these arguments, made by the company, underscore the importance of predominantly using the EQ-5D data from the IMCgp100-202 trial.
b) Due to the missing data from the EQ-5D-5L questionnaires on the IMCgp100-202 trial, data imputation was performed. Three imputation approaches were adopted by the company; data imputation was performed for baseline (mean imputation) and treatment phase (multiple imputation) but not for the survival follow-up period (i.e. assuming missingness is completely at random). However, the EAG considered that these approaches were not appropriately justified. Mean imputation should be avoided in general as it distorts the distribution of the imputated data in several ways. Particularly it can underestimate the variance and disturb relations between variables and biases any estimate other than the estimate of the mean, and the mean estimate itself when data is not missing completely at random (MCAR), as is most likely applicable in this case. As seen in CS Table 62 and Table 24 of the response to the clarification question, data are likely

not MCAR. Indeed, more data from the IC arm are missing before end-of-treatment, and more data from the tebentafusp arm are missing for survival follow-up and missingness increases with increasing trial follow-up. Moreover, for the survival follow-up period the company removed incomplete data prior to analysis which is known as listwise deletion or complete-case analysis. Listwise deletion potentially introduces inconsistencies in the data and if the data are not MCAR (as is most likely the case), listwise deletion can severely bias estimates of means, regression coefficients and correlations. Hence the imputation approach adopted by the company likely induces bias.

In addition to the flawed imputation, the company did not fulfil the request of clarification C10, where the EAG requested the company to use the original EQ-5D data from the IMCgp100-202 trial (using the Van-Hout crosswalk algorithm) without imputation and apply a generalised linear mixed model (taking into account the nested data) that includes the covariates that are considered in the data imputation, as well as the covariates for the on/off treatment, and for being PFS or PD, i.e. progression status. Furthermore, the EAG requested an updated economic model and scenario analyses wherein these data are used (without applying the time-to-death utility values) and including scenario analyses considering waning of treatment utility benefit for being on treatment.

The EAG considered the company's approach to be flawed and believes induces bias. In addition, the incomplete clarification responses from the company were not helpful in this respect and hence the EAG is unable to resolve this key issue in the EAG analyses. Furthermore, analyses of the EQ-5D-5L questionnaires from the IMCgp100-202 trial should ideally be performed for the PCP subgroup.

c) Despite, the ACD stated that the choice of approach to estimate utility values was unlikely to be an important driver of the cost-effectiveness, the EAG perspective remains unchanged. According to the EAG the time-to-death utility approach adopted in the CS base-case is flawed from multiple perspectives: i) it is inconsistent with the model structure and common modelling practices; ii) the implementation is not transparent; and iii) the approach lacks face validity.

   i. Utility values were estimated based on time-to-death rather than based on disease status. However, the EAG considered that this approach was not appropriately justified. The decision of using time-to-death utility values is based on two arguments: clinical experts' opinion and literature. Nevertheless, the company did not explain the methods used to gather clinical experts' opinion, nor explained the reasoning of the clinical experts for this assumption. Moreover, the two sources for this choice were based on advanced melanoma (Hatswell et al. 2014, and TA366), not advanced UM. In addition, in TA366 the use of time-to-death utilities was criticised by the EAG. Additionally, not implementing health state utilities differentiating between progression free and progressed disease arguably lacks face validity (as it does not reflect the decline in HRQoL after progression), is inconsistent with the model structure as well as common modelling practices. Given the increased post progression survival with tebentafusp, the use of time-to-death utilities is most likely not conservative.

   ii. To implement the time-to-death utilities in a partitioned survival model, the company stated to use an approach equivalent to tunnel states. Moreover, 'multipliers' were used to combine TA366 and IMCgp100-202 utility values. The EAG considered that these aspects (and the associated assumptions) related to the implementation of the time-to-death utilities were not appropriately explained and thus impedes the transparency of this approach.

   iii. The estimated time-to-death utility values from TA366 lack face validity as it leads to implausible high utility values. The CS base-case applies an age adjustment factor to the QALY calculation based on utility values of the UK population to implement the utility

decrement of age. Nevertheless, the on-treatment utility value of patients over the age of 62 years with metastatic UM (xxxx) is higher than the average utility value of the UK population between 55 to 65 years (0.82). The company acknowledged this limitation in the clarification letter response and provided results of a scenario analysis that capped the baseline utility value at the norm of the age group, indicating the impact of this is minimal. Nevertheless, the utility values used lacked face validity which might be related to the handling of EQ-5D IMCgp100-202 trial data (discussed above).

Given the above, the EAG believes the time-to-death utility approach adopted in the CS base-case is flawed and as highlighted above the incomplete clarification responses from the company were not helpful in this respect and hence the EAG is unable to resolve this key issue in the EAG analyses.

Given the above and consistent with the original EAG report, the EAG would prefer the company to: a) use EQ-5D data from the IMCgp100-202 trial (ideally based on the PCP subgroup), and b) fix the flawed data imputation.

## 1. Cost-effectiveness results

Given the EAG comments provided on CS addendum 2, the EAG preferred using used the generalised gamma distribution and the log-logistic distribution (producing an ICER range) for OS and the generalised gamma distribution for both PFS and TTD (same distribution for bother treatments for all three outcomes). Notably, the EAG could not produce the EAG consistent with the original EAG base-case as some functionality the EAG initially implemented in the economic model, e.g. monthly BSC costs per cycle in the PD health state, was not implemented in the updated company's model (this adjustment did increase the ICER by roughly [redacted] original ERG report Table 6.2). The EAG analyses are provided in Table 1.

**Table 1: Deterministic ERG base-case (without the fixing violation for post progression health state costs)**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|
| **Original EAG base-case 1 (Extrapolation of OS – generalised gamma)** | | | | | |
| Tebentafusp | [redacted] | [redacted] | | | |
| IC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Original EAG base-case 2 (Extrapolation of OS – log logistic)** | | | | | |
| Tebentafusp | [redacted] | [redacted] | | | |
| IC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Updated EAG base-case 1 (Extrapolation of OS – generalised gamma) – without the fixing violation for post progression health state costs** | | | | | |
| Tebentafusp | [redacted] | [redacted] | | | |
| Pembrolizumab | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Updated EAG base-case 2 (Extrapolation of OS – log logistic) – without the fixing violation for post progression health state costs** | | | | | |
| Tebentafusp | [redacted] | [redacted] | | | |
| Pembrolizumab | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; IC = investigator's choice; OS = overall survival; PFS = progression-free survival; QALY = quality adjusted life years; TTD = time to treatment discontinuation