Single Technology Appraisal

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

Committee Papers

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 stakeholders:

1. **DSU main report**:
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2. **Company response of DSU report from Immunocore**

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4. **Stakeholder comments form Melanoma Focus**

5. **Stakeholder comment form OcuMel**

6. **Clinical expert statment**

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

Expert Elicitation Main Report

Expert elicitation exercise in response to an upheld appeal (NICE technology appraisal ID1441, tebentafusp for advanced uveal melanoma)

REPORT BY THE DECISION SUPPORT UNIT

May 2024

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ABOUT THE DECISION SUPPORT UNIT

The Decision Support Unit (DSU) is based at the University of Sheffield with members at the Universities of York, Bristol, Leicester, Warwick and the London School of Hygiene and Tropical Medicine. The DSU is commissioned by The National Institute for Health and Care Excellence (NICE) to provide a research and training resource to support the Institute's Centre for Health Technology Evaluation Programmes. Please see our website for further information: nicedsu.org.uk

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ABBREVIATIONS

ACM	Appraisal committee meeting
BSC	Best supportive care
CM	Cutaneous melanoma
DSU	Decision Support Unit
DCO	Data cut-off
EAP	Expanded access programme
EAG	External Assessment Group
ITT	Intention to treat
HLA	Human leukocyte antigen
PCP	Pre-choice pembrolizumab
PFS	Progression-free survival
OS	Overall survival
RIO	Rational Impartial Observer
UM	Uveal melanoma
QoI	Quantity of Interest
TA	Technology appraisal
TTD	Time to treatment discontinuation

1. BACKGROUND

Two National Institute for Health and Care Excellence (NICE) appraisal committee meetings (ACMs) were held to discuss NICE single technology appraisal (TA) ID1441, tebentafusp for advanced uveal melanoma.[1] The draft final appraisal decision was that tebentafusp was not deemed to be cost-effective and would not be recommended for the Cancer Drugs Fund.[1]

An appeal hearing was held on 20 October 2023, which was upheld on several points. The upheld points related to the appeal panel's expectation that, faced with significant uncertainty, the input of experts should be particularly important in informing the committee's judgements. The upheld appeal points related specifically to "*the most appropriate choice, and interpretation of survival curve models to interrogate the available data, and the most appropriate means of allocating supportive care costs in the model*".[1]

2. APPROACHES USED TO ADDRESS UPHELD APPEAL POINTS

To address the two upheld appeal points, the NICE Decision Support Unit (DSU) was instructed by NICE to

1. Use a structured approach to elicit expert estimates of the expected survival of people with uveal melanoma treated with pembrolizumab and those treated with tebentafusp and the uncertainty around these estimates.
2. Consult expert opinion on the resources used in the provision of best supportive care (BSC) for people with uveal melanoma over the course of their disease after progression.

A structured expert elicitation approach was used for point 1, for which two workshops were conducted, one online and one face-to-face. An online survey was used to obtain expert opinion for point 2.

The DSU team was provided with all company and External Assessment Group (EAG) submissions and documents relating to the submission with full access to academic and clinical confidentiality data.

This report provides a brief commentary on the expert elicitation workshops and surveys conducted, in conjunction with the online and face-to-face expert elicitation workshop reports.[2, 3] In addition to this report, a one-page summary of the approaches employed is included for reference.[4]

Section 3 presents a description of the expert selection process for the elicitation workshops and online surveys. Section 4 describes the approach and methodologies for the workshops relating to overall survival. This includes construction of the Evidence Dossier, and an overview of the workshop format. For more detailed information on the workshop, please see the supporting workshop reports.[2, 3] Section 5 describes the consultation with experts regarding BSC resource use via an online survey. Section 6 presents the expert elicitation workshop results on the elicited overall survival at 8 years post-randomisation, along with a summary of expert opinions relating to BSC resource use. Section 7 concludes with a discussion of the elicitation workshop results and the online survey for BSC resource use.

3. EXPERT SELECTION

The identification of relevant experts, including clinical and medical oncologists, was first conducted by the DSU team, focussing on experts affiliated with specialist centres recommended by NICE. Input from the company, EAG, NICE and patient groups (Melanoma Focus and OcuMel) was subsequently sourced to ensure full coverage of the expert pool. The DSU team then complied a full list of potential experts based on all stakeholders' input (n=81*). Duplicate recommendations were removed and experts with prior involvement with TA ID1441 were excluded from participating, this could include attendance at either appraisal committee meeting (ACM) or advisory board meetings for this topic.

The remaining experts (n=52) were invited via email to participate in the elicitation workshop and online survey. Contact emails were either provided directly from the nominating party or identified from online sources. In the event that a contact email was not available, the nominating party was contacted for the experts' details. Out of the 52 experts invited to participate, 21 expressed an interest in participating in the workshops and/or survey. Out of the remaining 31 experts, three experts self-identified that their expertise would not be relevant to this appraisal, 18 experts did not respond, and 10 invitation emails were not deliverable due to expired or incorrect email addresses.

Following this, eligible expert availability responses were collated (n=21). Due to the high interest in participation, it was possible to schedule an online and a face-to-face workshop with two distinct cohorts of experts (n=6 and n=5, respectively). The workshops were subsequently scheduled according to expert availability and experts were contacted to submit confidentiality and consent declarations.

Experts (n=5) who were not able to take part in either the online or face-to-face workshop but expressed interest to complete the survey on BSC resource use, were also asked to submit confidentiality and consent declarations. Three of these experts completed the BSC survey. Experts participating in either the online or face-to-face workshop were also invited to complete the BSC survey. Nine of these experts completed the survey.

An expert selection flow diagram can be found in Appendix 1: Flow diagram of expert selection. A list of experts involved in the online, face-to-face and survey-based exercises is included in Appendix 2: Experts' expertise area and declaration of conflicts of interest, along with declared conflicts of interest and expertise.

4. ELICITATION OF LONG-TERM OVERALL SURVIVAL

4.1 Evidence Dossier compilation

The Evidence Dossier for the elicitation of long-term OS was developed by the DSU team. Data from the pivotal trial, IMCgp100-202, was sourced from the company directly. This included the pre-choice pembrolizumab (PCP) subgroup OS (data cut-off [DCO] June 2023), intention to treat (ITT) population progression-free survival (PFS, DCO August 2021) and PCP subgroup time to treatment discontinuation (TTD, DCO April 2022).

The company, EAG and relevant patient groups were consulted for additional supporting literature relevant to the elicitation workshops. The recommended literature included reviews of the method of action of tebentafusp, existing publications relating to the pivotal trial

* Number of experts includes duplicated recommendations.

(IMCgp100-202), as well as publications relating to potential comparator therapies and meta-analyses of existing therapies.

In addition to the twelve publications[5-16] recommended by the company, EAG and patient groups, an internal scoping search was conducted according to the criteria outlined in Appendix 3: Scoping search for Evidence Dossier. Publications were sifted according to the title and abstract and the remaining publications were reviewed using the full-text. This resulted in an additional two relevant studies relating to tebentafusp being identified.[17, 18] Finally, a forward citation search was conducted using the Rantala et al. 2019[13] paper as a seed paper in order to find any further studies relevant for the efficacy of the comparator for TA ID1441. Five additional relevant publications were identified from the citation search and included within the Evidence Dossier.[19-23]

The Evidence Dossier was sent for review by the company and experts prior to the commencement of the online and face-to-face workshops. The same Evidence Dossier[24] was used as reference for both the online and face-to-face workshops.

4.2 Workshop format

The elicitation of experts' judgements was conducted according to the Sheffield Elicitation Framework (SHELF) v4 protocol.[25] Training materials were designed as a combination of specific resources relevant to time-to-event outcomes as well as existing training materials provided as part of the SHELF protocol.

The format of the two workshops, online and face-to-face, was the same and is outlined below.

1. Training of experts in making probability judgements, extrapolating survival probabilities. One practice exercise on eliciting long-term survival data for lung cancer patients who quit smoking was also conducted.
2. Independent individual expert judgements on plausible limits, median, and upper/lower quartiles.
3. Presentation of individual judgements and scenario testing.
4. Group discussion – hazard trends, survival estimates, individual reflection.
5. Definition and discussion of rational impartial observer (RIO) judgements via behavioural aggregation*.

To clarify, as per the SHELF protocol, following the presentation of individual judgements and group discussion, the experts were asked to consider the perspective of a "Rational Impartial Observer", referred to as "RIO". RIO is assumed to have reviewed the Evidence Dossier and observed the individual judgements and subsequent group discussion. The experts were asked to agree on a set of probability judgements that such an observer would make, and it is the "RIO distribution" that is presented as the conclusion from the workshop.

5. CONSULTATION OF BSC RESOURCE USE

An online survey was sent to the experts who agreed to take part (n=15). A total of 12 experts responded to the online survey, 9 of these participated in either the online or face-to-face

* Note that mathematical aggregation was used for the initial proposal of a RIO distribution when experts' individual judgements were highly consistent.

elicitation workshops. The experts' conflicts of interest and expertise are included in Appendix 2: Experts' expertise area and declaration of conflicts of interest.

The survey covered the background on how BSC resource use was modelled by the company and EAG, see Appendix 4: BSC survey background provided to experts for the survey background provided to experts. The survey asked the following three questions:

1. Would patients start receiving BSC when they have progressed, irrespective of the level of deterioration in their quality of life?
2. Would the sub-population of longer-term survivors be receiving BSC after progression?
3. Would the rest of the population (i.e. non-long-term survivors) receive BSC after progression?

Additionally, an optional question was included to allow the experts to provide any additional information or comments relating to BSC in advanced uveal melanoma patients that they felt was relevant to TA ID1441.

6. RESULTS

6.1 Overall survival

The Quantities of Interests (QoIs) elicited in the online and face-to-face workshops were:

> **QoI 1**: for the pre-choice pembrolizumab (PCP) subgroup population from the IMCgp100-202 trial in **the tebentafusp arm**, the proportion of patients, expressed as a number per 1000, who would still be alive at year 8 after randomisation.
>
> **QoI 2**: for the pre-choice pembrolizumab (PCP) subgroup population from the IMCgp100-202 trial in **the pembrolizumab arm (excluding the effect of tebentafusp as a subsequent treatment)**, the proportion of patients, expressed as a number per 1000, who are still alive at year 8 after randomisation.

When expressing judgements for QoI1, the experts provided estimates assuming people would continue to receive tebentafusp via commercial product or the expanded access programme (EAP) after receiving tebentafusp via the pivotal trial. When expressing judgements for QoI 2, the experts accounted for subsequent treatments being received following pembrolizumab but excluded the potential effect of tebentafusp being received as a subsequent treatment.

The experts concluded that potential factors that could contribute to hazards of death that decrease over time include:

- A subgroup of longer-term survivors whose biology generally results in longer survival (irrespective of treatment received).
- Patients who progress radiologically and were treated with tebentafusp can appear to be doing well clinically.
- Patients who do respond to pembrolizumab may experience good disease control. Experts expressed that it is difficult to predict responders and therefore the clinical benefits for patients when treated with pembrolizumab.

Experts concluded that potential factors that could contribute to hazards of death that increase over time include:

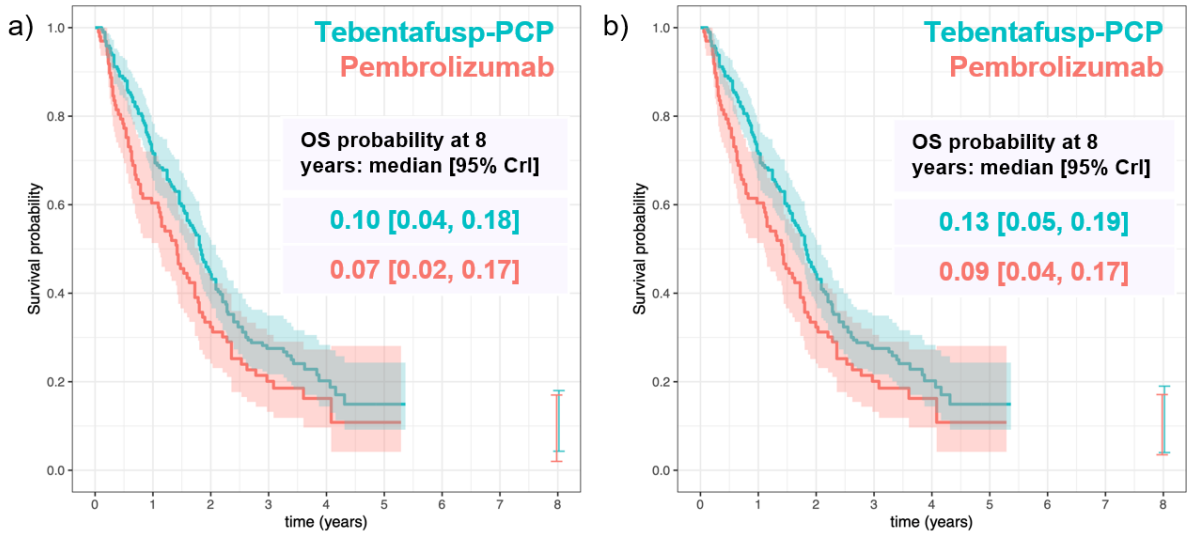
- Aging.
- Medical comorbidities.
- Less effective subsequent therapies.
- Volume of disease.
- Long-term toxicity effects (experts stated this to be unlikely for single-agent immunotherapies)

Tebentafusp was believed by all experts to be more effective than pembrolizumab with a difference in OS at 8 years. All experts were hesitant to suggest a cure potential due to the limited data.

Figure 1 presents the Kaplan-Meier curves for the PCP subgroup population from the IMCgp100-202 trial (DCO June 2023) for both treatment arms using reconstructed individual patient-level data and the elicited 95% credible intervals at 8 years. The percentiles from the fitted RIO distribution from both workshops are presented in Table 1.

The online group's RIO median and 95% credible interval for OS probability is 0.10 (0.04, 0.19) for the tebentafusp arm and 0.07 (0.02, 0.17) for the pembrolizumab arm. The face-to-face group's RIO median and 95% credible interval is 0.13 (0.05, 0.19) for the tebentafusp arm and 0.09 (0.04, 0.17) for the pembrolizumab arm.

Figure 1: Reconstructed OS data (DCO June 2023) with the plotted RIO 95% credible interval for the a) online workshop and b) face-to-face workshop



Abbreviations: RIO, Rational Impartial Observer; OS, overall survival; DCO, data cut-off; CrI, credible interval; PCP, pre-choice pembrolizumab.

Table 1: Percentiles of overall survival probability at 8 years post-randomisation from the fitted RIO distribution from both workshop groups

Percentile	1%	2.5%	10%	25%	50%	75%	90%	97.5%	99%
Online (Tebentafusp)	0.04	0.04	0.06	0.08	0.10	0.12	0.15	0.18	0.20
Face-to-face (Tebentafusp)	0.03	0.05	0.08	0.10	0.13	0.15	0.17	0.19	0.20

Percentile	1%	2.5%	10%	25%	50%	75%	90%	97.5%	99%
Online (Pembrolizumab)	0.02	0.02	0.04	0.05	0.07	0.10	0.13	0.17	0.19
Face-to-face (Pembrolizumab)	0.03	0.04	0.05	0.07	0.09	0.11	0.14	0.17	0.19

Abbreviations: RIO, Rational Impartial Observer.

6.2 BSC resource use

Different approaches were used to apply BSC associated costs within the economic model by the company and EAG. The company based their approach on the study by McKendrick et al. 2016,[26] where BSC is shown to be provided for an average of 4 months for patients with metastatic melanoma. Based on this, the entire cohort of patients within the trial is assumed to receive BSC for an average of 4 months. Within the model, the costs associated with BSC are applied as a one-off cost at the point of progression of patients. This approach applies the one-off 4-month BSC cost to all progressed patients, irrespective of how long they then spend within the progressed state. The company also include end-of-life costs to reflect the additional management of patients within the final year of life.

The EAG believed that costs associated with BSC would be dependent on the time between progression and death and therefore opted to apply BSC costs monthly to reflect this. In response to company concerns of double-counting of end-of-life costs through the implementation of monthly BSC costs, the EAG removed end-of-life costs from the model.

The experts were asked to fill in an online survey with questions relating to the administration/referral of BSC to patients with advanced UM after progression. The experts' responses to the online survey were collated and are summarised below. The full anonymised expert responses to the BSC survey are included in

Appendix 5: Healthcare resources use survey response for reference.

The experts were asked whether patients would receive BSC after radiological progression irrespective of their fitness status. Multiple experts reported that patients would be referred to community palliative care centres irrespective of their deteriorative status in order to start building relationships with the palliative care team and start developing individualised care plans. The experts also noted that patients who are relatively well at the time of progression may be referred to the palliative care unit but may not engage with the unit until “the point of clinical need”. The experts expressed that all patients would continue to receive regular reviews/scans, irrespective of their level of deterioration in order to monitor their disease and best adapt their care regimen. The expert responses largely referred to the symptomatic status and how this would correlate with BSC resource usage. If patients display symptoms at the time of progression, then BSC would be provided. For patients who appear well, with minimal symptoms, alternative therapies or trial enrolment would be considered ahead of BSC. The experts ultimately expressed that the referral of patients for BSC and their level of interaction (and therefore associated resource use) is variable and that BSC is considered on an individual basis according to the symptomatic status of the patient.

In the elicitation workshops for the OS quantities of interest, it was evident that within the population of advanced UM patients, there is a subgroup of longer-term survivors. The experts were asked specifically about the allocation of BSC resources for this subgroup of patients. As for the first question, the experts expressed that BSC referral is on an individualised basis, but ultimately expressed that patients would be referred for BSC if they were symptomatic. Here some conflicting opinions regarding this subgroup of patients arose. One expert expressed that patients within this subgroup are unlikely to be symptomatic whereas another expert stated that it is unlikely for these patients to be symptom free and thus they would be receiving BSC. Overall, it appeared that these diverging opinions result from the highly variable presentation of the disease in this small subgroup of advanced UM patients, and that ultimately BSC would be recommended for symptomatic patients.

With reference to the non-longer term surviving patients, who make up the majority of the patient group, the experts stated that the disease in these patients is likely to be more aggressive (hence reduced survival times), and thus BSC is required sooner after radiological progression. Again, this was dependent on the symptomatic status of the patients. A range of durations of BSC were provided by the experts, spanning a few weeks to twelve months. This large range of times was reflected by additional comments from experts which discussed the broad range of support encompassed by BSC, including low-level advice up to major 24-hour care. The experts believed that the intensity of BSC resource use would increase in the final months of life, and that for some patients BSC immediately after radiological progression, BSC use will be minimal due to the lack of symptoms.

The experts were also given the opportunity to add any other relevant information in an optional question, to which some experts expressed the difficulty of defining “BSC” as it covers a broad range of patient support, some of which is considered standard and would be conducted in conjunction to systematic anti-cancer treatments prior to progression.

To summarise, the experts expressed that patient referral for BSC is an individualised decision based on patient symptoms. Even fit and well patients who have not yet deteriorated, may be referred to palliative care units to start planning later support. All patients will continue to have regular reviews in order to monitor their disease progression irrespective of their level of deterioration.

7. DISCUSSION

7.1 Overall survival

At ACM2, the company's base case was based on a comparison of tebentafusp with pembrolizumab in the PCP subgroup using survival data from the April 2022 data cut-off from the IMCgp100-202 trial. The company preferred to use a piecewise modelling approach to extrapolate survival for the tebentafusp arm, where the Kaplan-Meier estimate was used for the first phase (up to 28 months) followed by a lognormal distribution to model the second phase (from 28 months onwards). For the pembrolizumab arm, a standard parametric model was used, the company preferred to use a Weibull distribution (non-piecewise approach). The EAG presented two base case scenarios, both of which used standard parametric models and did not adopt the piecewise approach. The EAG preferred to use the same parametric model in both arms. In base case 1, the EAG used the generalised gamma distribution to model both arms, and in base case 2 the EAG used the log-logistic model for both arms. The company and EAG predicted OS probabilities at 8 years post-randomisation are shown in Table 2. The most recent OS data (April 2024) for the ITT population can be found in Appendix 6: Overall survival (April 2024 data cut) for intention to treat population

Question 1					
1. Would patients start receiving BSC when they have progressed, irrespective of the level of deterioration in their quality of life? For example: would a still well and fit patient with progressed disease receive BSC? Please provide your answer along with relevant justification.					
Expert	**Response**				
1	would aim to offer active treatment or clinical trial enrolment to fit and well patients rather than best supportive care unless they were not suitable for treatment				
2	No, a fit patient would not be receiving resource as BSC				
3	No - not if asymptomatic. Would be monitored fir deterioration and signposted				
4	No, if a patient had progressed but was asymptomatic I would not involve the specialist palliative care team. I would signpost them that this may be required in the future and practically what that may involve.				
5	No - a fit and well patient would be for consideration of subsequent therapy lines and this would mean either with the ongoing support from their CNS/team or trials team rather than a BSC pathway. They may also choose not to have treatment at this point and would also not be using BSC resources if fit and well - they would continue to be able to access psychological support from their CNS.				
6	Best supportive care is a phrase to include any support that is not directly about treating the cancer. All patients should be offered best supportive care even if fit and well - however their care needs could be very little at this stage. I would usually refer to the Palliative Care Team highlighting the absence of physical symptoms but also the great uncertainty and the poor prognosis. They are very likely to be offered formal or informal psychological support, plus practical help with eg finances, advanced care planning etc. It is essential the patient does not feel 'abandoned' just because there is no specific anti-cancer treatment for them. It is also important that it is clear who has overall responsibility for their care. This may continue to rest with Oncology (most likely, particularly if they are well, as they are likely to find ongoing monitoring helpful to give insight into the pace of the disease) or be officially taken over by the Palliative Care Team, or revert to the GP with facilitated rapid access back to either team in the event of deterioration.				

7	This is not a binary yes/no question: all patients should receive BSC either alone or in addition to SACT. It is not clear to me what your underlying question actually is.
8	No, patients would receive BSC at the point of clinical need, indicated by symptomatic deterioration in quality of life. This may not be the case at the point of disease progression, a parameter identified radiologically.
9	Yes- an offer of BSC forms background support for all patients but the degree of support required may be minimal in the earlier stages of progression
10	When patients' radiologically progressed and if there is no further active treatment available, ,these patients are started on BSC, which involves informing community services (district nurses, McMillan nurses, GP,etc) and introducing their service to these patient.This also means their in-hospital treatment will be tailored to their needs.(Palliative team review,psychological services ,etc) However,If the patient is fit-enough, they usually do not use these services until they feel the need for help. Whole point of starting the patient on BSC when they progressed, is to make sure these services are in-place for them, as and when the necessity arises.
11	Yes, we aim to refer patients at the point of progression to community palliative care to start building BSC support - even if the pt is fit, its important to start building relationships and the duration of time the pt may remain fit is v unpredictable but generally short. The term 'BSC' covers a very wide range of support, from low level advice, sign posting and safety netting, to major 24 hour end of life care, which I suspect is part of the problem when trying to allocate costs. The intensity of costs will be particularly high in the last 1-3 months of life.
12	Yes, they will receive regular review and any intervention needed. It's unclear what is meant by BSC but this will include regular review and probably regular scans. when patients become symptomatic, they will have further symptomatic treatment e.g. steroids and analgesia. The cost of this will not be the same for every patient and will change with time within a patient group.

Question 2					
2. Would the sub-population of longer-term survivors be receiving BSC after progression? If yes, how long after progression would they begin receiving BSC and on average, how long for? Please provide your answer along with relevant justification.					
Expert	**Response**				
1	best supportive care is aimed at controlling symptoms and optimising quality of life, the duration of BSC would need to be individualised depending on presence/ absence of symptoms. It is likely that those with progression would need ongoing BSC until death from disease or the development of a suitable treatment for them				
2	Thye would recieve BSC when they had symptoms needing palliation, however this can be for a number of months, depending on rate of progression				
3	No, for reasons as above, not until symptoms				
4	No, not unless they had complex symptoms requiring additional support. Most of the patients achieving long term survival after progression have been asymptomatic and well.				
5	This is an answer which is almost impossible to give with any accuracy due to the very variable disease course in patients who have longer term survival, particularly those who have response to any subsequent therapy.				

	Patients may go on being well for months/years post an initial progression of disease and not require any access to BSC type resources. Often patients do not wish to access BSC resources until they have specific issues requiring input and this is a very individual factor. Average time on BSC for this group can also be very variable and I do not think its possible to give an accurate frame for this - but probably around 3-6 months.
6	Radiological progression does not necessarily correlate with survival for patients treated with Tebentafasup. Therefore formally moving onto BSC (and involvement of the Palliative Care Team) requires case-by-case assessment and is unlikely to be suitable for everyone. If a patient is clinically well, tolerating treatment and has no significant cancer-related symptoms then even with progression on scan, they are more likely to continue under the care of the Oncology Team and remain on Tebentafusp. If a patient is progressing clinically or symptomatically, then they would move onto BSC and this is likely to be needed for 3-6 months usually.
7	This and the previous question makes be wonder whether you mean something other than literal Best Supportive Care.
8	Yes, at least a proportion of this sub-population would receive BSC after progression. From experience the sub-population of longer-term survivors would however receive BSC at a later time point following disease progression, as it is more likely for them to remain asymptomatic, or minimally symptomatic, with preserved quality of life, for a longer period of time. A small proportion may not require BSC. I do not feel able to put an average time on this, given the small patient numbers.
9	Yes- an offer of BSC forms background support for all patients including long term survivors but the degree of support required may be minimal until the more advanced symptomatic stage which may be a short number of years after progression
10	The answer is Yes, and all patients start on BSC after the progression. In my experience these patients access these services when they are clinically deteriorating . On average they receive BSC for the final 3-4 months of their lives.
11	These are rare patients. The fact that they have progressed brings with it much angst and few patients are symptom-free, to they will likely be referred for BSC alongside also maintaining their secondary care team links
12	The answer is as for 1 above. Patients with progressive disease will have ongoing review. Some will be asymptomatic for a period of time, others will have symptoms, but they will have regular review.

Question 3					
3. Would the rest of the population (i.e. non-long-term survivors) receive BSC after progression? If yes, how long after progression would they begin receiving BSC and on average, how long for? Please provide your answer along with relevant justification.					
Expert	**Response**				
1	yes probably 6-12 months				
2	Yes, see answer above				
3	Yes around 6 months				
4	BSC in the face of symptomatic progression is generally required for a short period time perhaps weeks to short months prior to death.				

5	This population tend to have more rapidly progressive disease - start BSC at the point of progression often and are using the resources for around 3 months on average.
6	Patients with confirmed progression with no options for treatment of their ocular melanoma would move onto BSC. I would usually arrange this at the point at which progression is confirmed, if I had not arranged it in advance. On average they are likely to receive this for 3-6 months but there is significant variability.
7	Sorry, makes no sense.
8	Yes, the non-long term survivors would receive BSC after progression. By definition, if survival is shorter, the disease is likely to behave more aggressively and therefore result in clinical symptoms and an associated deterioration in quality of life much sooner. It is difficult to be precise regarding when BSC would be required, but it is likely to be within days to weeks of disease progression and continue for a short number of months (2-4).
9	Yes. BSC initiated at the point of progression and duration would be for the anticipated life expectancy (median 9-12 months)
10	Yes they will, and these patients will be started on BSC on noticing radiological progression. At this point, some of these patients already show clinical signs of disease progression and more likely to receive BSC almost immediately. Rest of the cases start to deteriorate in few weeks, after the radiological progression is noticed and to start using the services. These patients usually receive BSC for around 2-3 months.
11	Yes - immediately and might be 3-4 months on average.
12	Yes, as for above.

Appendix 6: Overall survival (April 2024 data cut) for intention to treat population for reference.

Table 2: Company and EAG predicted 8-year OS probabilities using the April 2022 DCO, PCP subgroup data

	Precited 8-year OS probability	
	Tebentafusp-PCP	**Pembrolizumab**
Company	0.199	0.006
EAG (generalised gamma)	0.043	0.044
EAG (log-logistic)	0.076	0.062

Abbreviations: EAG, External Assessment Group; OS, overall survival; DCO, data cut-off; PCP, pre-choice pembrolizumab.

The experts from both workshops expressed the same opinions around factors that may contribute to decreasing or increasing hazards of death for the modelled patient groups. No contradicting opinions were observed. The plausible ranges for survival proportions at 8 years elicited from the two workshops are consistent with each other. For instance, both groups believed it not to be plausible that the 8-year OS probability would be less than 0.03/0.04 for the tebentafusp-PCP arm and 0.02/0.03 for the pembrolizumab arm. Similarly, it was not considered plausible that the 8-year OS probability would exceed 0.2 for the tebentafusp-PCP arm and 0.19 for the pembrolizumab arm.

The face-to-face group was generally more optimistic than the online group for both treatment arms, despite the overall plausible ranges elicited being similar to those from the online group. This was reflected by the medians of the RIO distributions. The RIO medians for the tebentafusp-PCP arm for the face-to-face and online workshops were 0.13 and 0.10, respectively and the RIO medians for the pembrolizumab arm were 0.09 and 0.07, respectively.

7.2 BSC resource use

The company and EAG used different approaches to apply BSC associated costs within the economic model used in TA ID1441. The company based their approach on the study by McKendrick et al. 2016,[26] and implemented BSC costs as a one-off cost equating to the costs associated with 4-months BSC resource use. This approach applies BSC costs in a way that is independent of the amount of time spent within the progressed disease state. In contrast, the EAG applied BSC costs as a monthly cost, such that they are dependent on the amount of time spent in the progressed disease state. The company included end-of-life costs within the model, but the EAG, in response to company concerns around double counting, removed these costs from their model.

Generally, there were mixed views from experts on the allocation of BSC use at the time of radiological progression. The experts highlighted that the difference in BSC resource use would be according to patient symptomatic status. Patients who exhibit symptoms associated with progression would require palliative care and further monitoring, whereas those who are asymptomatic would be monitored for deterioration and the development of progression-associated symptoms but otherwise may not receive other aspects of BSC. Some experts did highlight that all patients (irrespective of their symptomatic status) would be referred to community palliative care units to start building relationships and planning long-term care regimes.

With reference to long-term surviving patients, the experts also highlighted that BSC resource use is largely based on the presented symptoms of patients. The remaining patients (non-long-term survivors) were generally expected to receive BSC after progression, however this

would still be dependent on their symptomatic status. The experts expressed that the duration that BSC would be provided for would be correlated with the severity/complexity of symptoms presented at progression.

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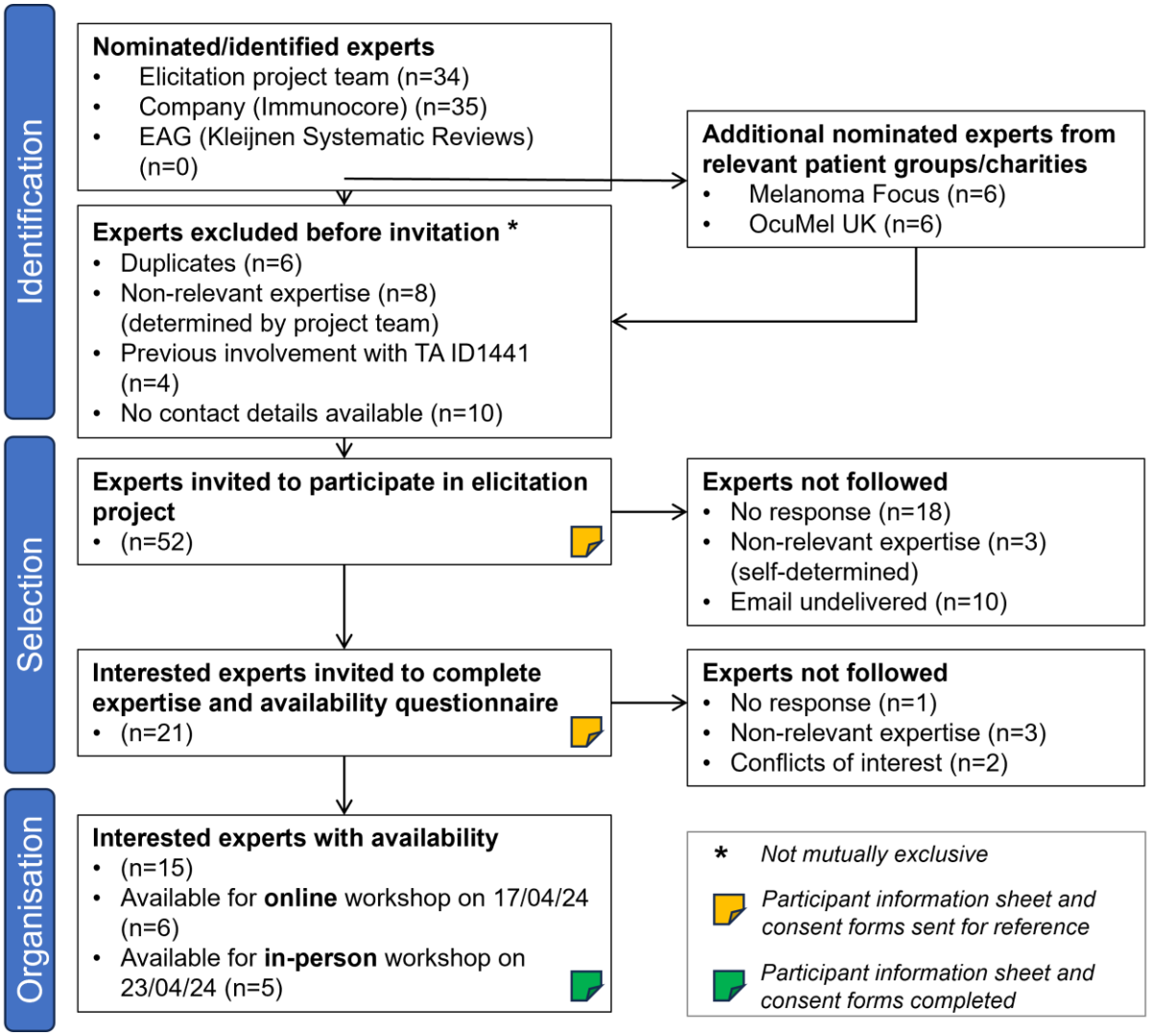
APPENDIX 1: FLOW DIAGRAM OF EXPERT SELECTION



APPENDIX 2: EXPERTS' EXPERTISE AREA AND DECLARATION OF CONFLICTS OF INTEREST

Online elicitation workshop for overall survival		
Expert name	**Expertise Area**	**Conflicts of interest**
Dr Jenny Nobes	Consultant Oncologist since 2010. (Norfolk and Norwich University Hospital)	Received honorarium May 2023 from Immunocore for talk at Melanoma Focus meeting.
Dr Bode Oladipo	Consultant Medical Oncologist treating melanoma including uveal. 12.5 years experience. (Belfast Health and Social Care trust)	Received honorarium for participation in advisory board and educational meetings from both Merck Sharp & Dohme and Bristol-Myers Squibb. Involved in the national tebentafusp expanded access programme.
Dr Lalit Pallan	Consultant Medical Oncologist, specialising in Melanoma. In post since 2020. See patients with high risk of primary uveal melanoma to co-ordinate follow up and screening investigations for metastatic disease. (University Hospitals Birmingham NHS FT)	Received speaker fees from Bristol-Myers Squibb. PI on Immunocore clinical trial in cutaneous melanoma – ongoing (MEL-203).
Dr Kate Scatchard	13 years of experience. Undertake surveillance for a larger cohort of uveal melanoma patients. (Royal Devon University Hospitals NHS Trust)	None
Dr Patricio Serra	Consultant Medical Oncologist, experience in the field of melanoma for over 8 years. Experience with patients with melanoma, cutaneous, mucosal and uveal in the early stages and advanced stages of cancer. Specialist Skin Multi-disciplinary team (SSMDT) chair where the management of melanoma cases are discussed. (The Christie NHS Foundation Trust)	Fees received as Speaker for Bristol-Myers Squibb.
Dr Heather Shaw	Consultant medical oncologist treating melanoma and skin cancers with a specific interest in UM. Consultant for 7 years. Currently the National Coordinating Investigator for two clinical trials with a specific focus on UM. A contributing oncologist to national UM guidelines. Treated many patients with	Provided speaker services, advisory board input and has run/ is running clinical trials for Bristol-Myers Squibb, Immunocore, Merck Sharp & Dohme. No involvement in any advisory meetings on the current appraisal to date (ID1441).

	tebentafusp (and with its cousin molecule in development) and have significant experience of the clinical pathway these patients follow. (University College London Hospitals and Mount Vernon Cancer Centre)	Registered practitioner on previously available tebentafusp EAP in UK (now closed). National Coordinating Investigator for F106C Phase I study (multiple tumour types) and Principal Investigator on PRISM-301 (cutaneous melanoma), steering committee member for TebeAM (cutaneous melanoma).

Face-to-face elicitation workshop for overall survival		
Expert name	**Expertise Area**	**Conflicts of interest**
Dr Clare Barlow	Medical Oncology consultant. Immunotherapy Service Lead for SFT. Provides liver surveillance for high risk ocular melanoma patients and treatment for metastatic disease for almost 15 years (since July 2009). (Somerset Foundation Trust)	Sponsorship for educational meetings/Advisory Board honoraria/speaker fees Merck Sharpe Dohme and Bristol Myers Squibb.
Dr Steve Nicholson	Consultant oncologist with responsibility for management of melanoma (cutaneous & non-cutaneous) and rare urological malignancy (testis, penis, renal). 22 years experience managing melanoma at consultant level. (Mid & South Essex NHS Foundation Trust)	None
Dr Miranda Payne	Consultant Medical Oncologist specialising in melanoma for the last 10 years. (Oxford University Hospitals NHS Foundation Trust)	Speaker fees and funding to attend conferences from Bristol-Myers Squibb and Merck Sharp & Dohme.
Dr Rachel Plant	Consultant Medical Oncologist with interest in melanoma for 5 years. (University Hospital Dorset)	None
Dr Dulani Ranatunge	Consultant Medical Oncologist. Manages skin cancers, specialising in melanoma including uveal melanoma for 6 years. (Queens Center for Oncology, Hull University teaching Hospital)	None

Healthcare resource use online survey		
Expert name	**Expertise Area**	**Conflicts of interest**
Dr Clare Barlow	Medical Oncology consultant. Immunotherapy Service Lead for SFT. Provides liver surveillance for high risk ocular melanoma patients and treatment for metastatic disease for almost 15 years (since July 2009). (Somerset Foundation Trust)	Sponsorship for educational meetings/Advisory Board honoraria/speaker fees Merck Sharpe Dohme and Bristol Myers Squibb.
Dr Pippa Corrie	Consultant medical oncologist, >25 years experience. (Cambridge University Hospitals NHS Foundation Trust)	Previously conducted the phase I and II trials evaluating tebentafusp.
Professor Paul Lorigan	Consultant oncologist specialising in melanoma > 20 years. (University of Manchester and Christie NHS Foundation Trust)	Paid speaker for Bristol-Myers Squibb and Merck Sharp & Dohme.
Dr Steve Nicholson	Consultant oncologist with responsibility for management of melanoma (cutaneous & non-cutaneous) and rare urological malignancy (testis, penis, renal). 22 years experience managing melanoma at consultant level. (Mid & South Essex NHS Foundation Trust)	None
Dr Jenny Nobes	Consultant Oncologist since 2010. (Norfolk and Norwich University Hospital)	Received honorarium May 2023 from Immunocore for talk at Melanoma Focus meeting.
Dr Bode Oladipo	Consultant Medical Oncologist treating melanoma including uveal. 12.5 years experience. (Belfast Health and Social Care trust)	Received honorarium for participation in advisory board and educational meetings from both Merck Sharp & Dohme and Bristol-Myers Squibb. Involved in the national tebentafusp expanded access programme.
Dr Miranda Payne	Consultant Medical Oncologist specialising in melanoma for the last 10 years. (Oxford University Hospitals NHS Foundation Trust)	Speaker fees and funding to attend conferences from Bristol-Myers Squibb and Merck Sharp & Dohme.
Dr Rachel Plant	Consultant Medical Oncologist with interest in melanoma for 5 years. (University Hospital Dorset)	None
Professor Ruth Plummer	Experience in systemic therapies for all types of	Participation in educational meetings for Bristol-Myers

	melanoma and has led the practice for ~20 years. (Newcastle University and Newcastle Hospitals NHS Foundation Trust)	Squibb and Merck Sharp & Dohme and conference travel funding from both of the above.
Dr Dulani Ranatunge	Consultant Medical Oncologist. Manages skin cancers, specialising in melanoma including uveal melanoma for 6 years. (Queens Center for Oncology, Hull University teaching Hospital)	None
Dr Kate Scatchard	13 years of experience. Undertake surveillance for a larger cohort of uveal melanoma patients. (Royal Devon University Hospitals NHS Trust)	None
Dr Heather Shaw	Consultant medical oncologist treating melanoma and skin cancers with a specific interest in UM. Consultant for 7 years. Currently the National Coordinating Investigator for two clinical trials with a specific focus on UM. A contributing oncologist to national UM guidelines. Treated many patients with tebentafusp (and with its cousin molecule in development) and have significant experience of the clinical pathway these patients follow. (University College London Hospitals and Mount Vernon Cancer Centre)	Provided speaker services, advisory board input and has run/ is running clinical trials for Bristol-Myers Squibb, Immunocore, Merck Sharp & Dohme. No involvement in any advisory meetings on the current appraisal to date (ID1441). Registered practitioner on previously available tebentafusp EAP in UK (now closed). National Coordinating Investigator for F106C Phase I study (multiple tumour types) and Principal Investigator on PRISM-301 (cutaneous melanoma), steering committee member for TebeAM (cutaneous melanoma).

APPENDIX 3: SCOPING SEARCH FOR EVIDENCE DOSSIER

Search 1: TEBENTAFUSP

Embase 1974 to 2024 Week 04

#	Searches	Results
1	(tebentafusp or kimmtrak or IMCgp100).mp.	290
2	(long-term or "long term").tw.	1398117
3	((extrapolat* or probabilit*) adj3 survival).tw.	20420
4	2 or 3	1415111
5	1 and 4	19
6	1 and 2	19

Search 2: PEMBROLIZUMAB

Embase 1974 to 2024 Week 04

#	Searches	Results
1	(pembrolizumab or lambrolizumab or Keytruda or MK-3475 or MK3475 or MK 3475 or L01XC18).mp.	41666
2	(advance* or metasta* or recurr* or unresect*).mp.	3477419
3	exp eye tumor/ or exp melanoma/ or exp uvea tumor/ or exp choroid tumor/	239923
4	melanoma.mp.	255058
5	exp eye/ or exp uvea/ or exp iris/ or exp choroid/	468053
6	(uvea or ocular or iris or choroid or eye).tw.	525785
7	(3 or 4) and (5 or 6)	26551
8	1 and 2 and 7	211
9	(long-term or "long term").tw.	1398117
10	((extrapolat* or probabilit*) adj3 survival).tw.	20420
11	9 or 10	1415111
12	8 and 11	15

APPENDIX 4: BSC SURVEY BACKGROUND PROVIDED TO EXPERTS

The text below is that which was provided to experts completing the BSC online survey.

Expert consultation for NICE TA for tebentafusp for uveal melanoma (ID1441) - best supportive care (BSC) resource use

We are aiming to obtain your opinions on the health care resources consumed by people with advanced uveal melanoma (UM) after disease progression.

The company that sponsored the tebentafusp evidence submission to NICE consulted with two UK clinicians to identify the mainstay activities for the management of advanced UM patients. Resources associated with brain/bone metastases and radiotherapy were deemed irrelevant within best supportive care (BSC). Resources related to management of liver metastases and consultations with ophthalmic surgeons were deemed relevant. In the company submission BSC resources were broadly described to include:

- medical consultations (medical oncologist consultation, oncology nurse visit, GP consultation, psychology specialist consultation, surgeon consultation),
- hospital visits (inpatient stay [oncology/general ward], emergency department visit, day hospital visit, ophthalmic surgeon consultation),
- procedures (surgical intervention).

During the NICE appraisal for tebentafusp, different approaches were used to apply BSC associated costs within the economic model. The assumptions preferred by the manufacturer of tebentafusp and those preferred by the External Assessment Group (EAG) are outlined below:

Company: based their approach on the study by McKendrick et al. 2016[26], where BSC is shown to be provided for an average of 4 months for patients with metastatic melanoma. Based on this, the entire cohort of patients within the trial is assumed to receive BSC for an average of 4 months. Within the model, the costs associated with BSC are applied as a one-off cost at the point of progression of patients. This approach applies the one-off 4-month BSC cost to all progressed patients, irrespective of how long they then spend within the progressed state. The company also include end-of-life costs to reflect the additional management of patients within the final year of life.

EAG: believe that costs associated with BSC would be dependent on the time between progression and death and therefore opted to apply BSC costs monthly to reflect this. In response to company concerns of double-counting of end-of-life costs through the implementation of monthly BSC costs, the EAG removed end-of-life costs from the model.

Note: at the second NICE committee meeting, the EAG were no longer able to implement their preferred application of BSC costs due to changes to the model. The impact of the EAG preferred application of BSC costs on the incremental cost effectiveness ratio (ICER) is therefore uncertain.

We would like you to answer the following three questions, using your own experience in treating patients with advanced UM as a reference. If you would like to provide any further comments please add these to the optional last question. For any queries regarding this survey please contact the project lead Kate Ren (s.ren@sheffield.ac.uk).

We are striving to make our work transparent and so would like to highlight that we aim to include all participants' names, affiliations, high-level descriptions of expertise and conflicts of interest within any subsequent reports/publications, as outlined in the consent form.

Thank you for your participation.

APPENDIX 5: HEALTHCARE RESOURCES USE SURVEY RESPONSE

Question 1	
1. Would patients start receiving BSC when they have progressed, irrespective of the level of deterioration in their quality of life? For example: would a still well and fit patient with progressed disease receive BSC? Please provide your answer along with relevant justification.	
Expert	**Response**
1	would aim to offer active treatment or clinical trial enrolment to fit and well patients rather than best supportive care unless they were not suitable for treatment
2	No, a fit patient would not be receiving resource as BSC
3	No - not if asymptomatic. Would be monitored fir deterioration and signposted
4	No, if a patient had progressed but was asymptomatic I would not involve the specialist palliative care team. I would signpost them that this may be required in the future and practically what that may involve.
5	No - a fit and well patient would be for consideration of subsequent therapy lines and this would mean either with the ongoing support from their CNS/team or trials team rather than a BSC pathway. They may also choose not to have treatment at this point and would also not be using BSC resources if fit and well - they would continue to be able to access psychological support from their CNS.
6	Best supportive care is a phrase to include any support that is not directly about treating the cancer. All patients should be offered best supportive care even if fit and well - however their care needs could be very little at this stage. I would usually refer to the Palliative Care Team highlighting the absence of physical symptoms but also the great uncertainty and the poor prognosis. They are very likely to be offered formal or informal psychological support, plus practical help with eg finances, advanced care planning etc. It is essential the patient does not feel 'abandoned' just because there is no specific anti-cancer treatment for them. It is also important that it is clear who has overall responsibility for their care. This may continue to rest with Oncology (most likely, particularly if they are well, as they are likely to find ongoing monitoring helpful to give insight into the pace of the disease) or be officially taken over by the Palliative Care Team, or revert to the GP with facilitated rapid access back to either team in the event of deterioration.
7	This is not a binary yes/no question: all patients should receive BSC either alone or in addition to SACT. It is not clear to me what your underlying question actually is.
8	No, patients would receive BSC at the point of clinical need, indicated by symptomatic deterioration in quality of life. This may not be the case at the point of disease progression, a parameter identified radiologically.
9	Yes- an offer of BSC forms background support for all patients but the degree of support required may be minimal in the earlier stages of progression
10	When patients' radiologically progressed and if there is no further active treatment available, ,these patients are started on BSC, which involves informing community services (district nurses, McMillan nurses, GP,etc) and introducing their service to these patient.This also means their in-hospital treatment will be tailored to their needs.(Palliative team review,psychological services ,etc) However,If the patient is fit-enough, they usually do not use these

	services until they feel the need for help. Whole point of starting the patient on BSC when they progressed, is to make sure these services are in-place for them, as and when the necessity arises.
11	Yes, we aim to refer patients at the point of progression to community palliative care to start building BSC support - even if the pt is fit, its important to start building relationships and the duration of time the pt may remain fit is v unpredictable but generally short. The term 'BSC' covers a very wide range of support, from low level advice, sign posting and safety netting, to major 24 hour end of life care, which I suspect is part of the problem when trying to allocate costs. The intensity of costs will be particularly high in the last 1-3 months of life.
12	Yes, they will receive regular review and any intervention needed. It's unclear what is meant by BSC but this will include regular review and probably regular scans. when patients become symptomatic, they will have further symptomatic treatment e.g. steroids and analgesia. The cost of this will not be the same for every patient and will change with time within a patient group.

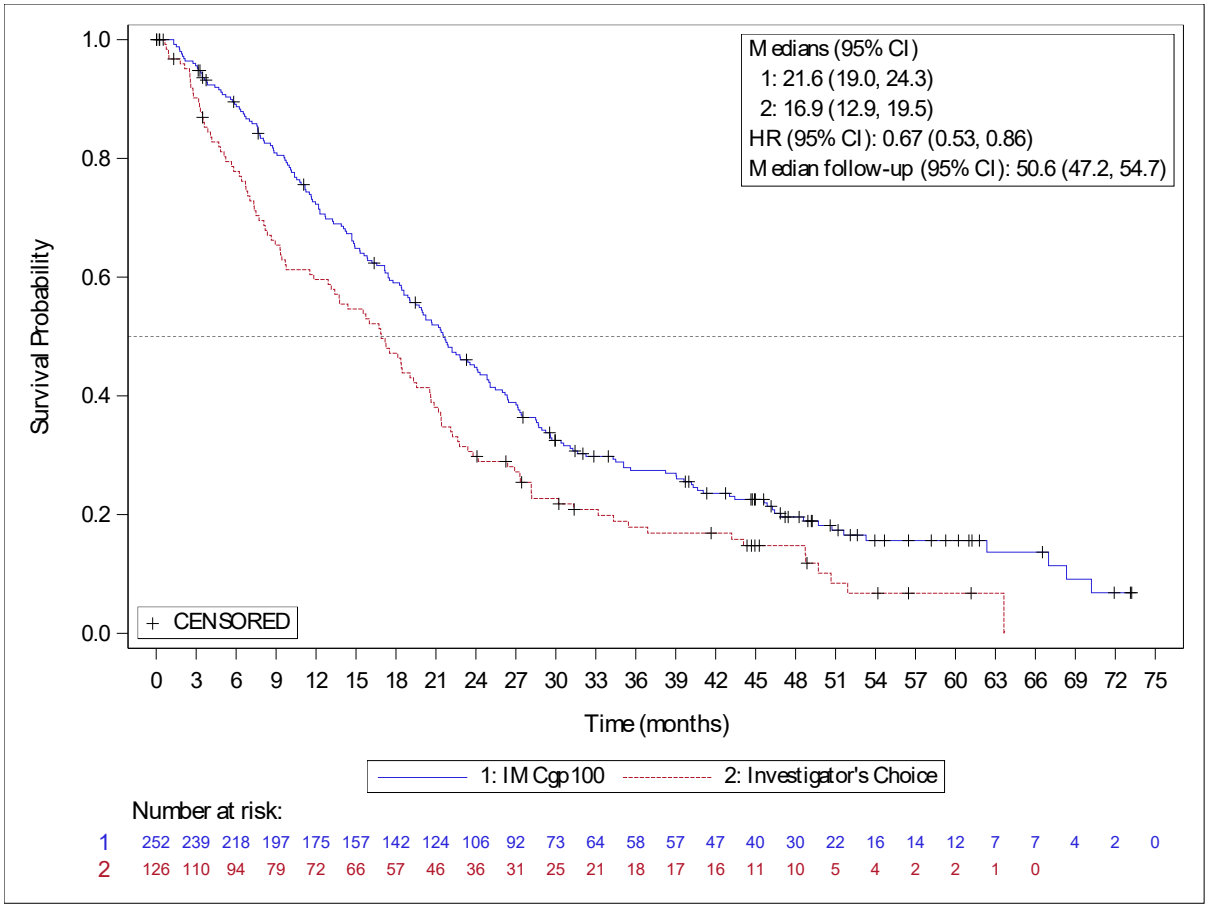
Question 2					
2. Would the sub-population of longer-term survivors be receiving BSC after progression? If yes, how long after progression would they begin receiving BSC and on average, how long for? Please provide your answer along with relevant justification.					
Expert	**Response**				
1	best supportive care is aimed at controlling symptoms and optimising quality of life, the duration of BSC would need to be individualised depending on presence/ absence of symptoms. It is likely that those with progression would need ongoing BSC until death from disease or the development of a suitable treatment for them				
2	Thye would recieve BSC when they had symptoms needing palliation, however this can be for a number of months, depending on rate of progression				
3	No, for reasons as above, not until symptoms				
4	No, not unless they had complex symptoms requiring additional support. Most of the patients achieving long term survival after progression have been asymptomatic and well.				
5	This is an answer which is almost impossible to give with any accuracy due to the very variable disease course in patients who have longer term survival, particularly those who have response to any subsequent therapy. Patients may go on being well for months/years post an initial progression of disease and not require any access to BSC type resources. Often patients do not wish to access BSC resources until they have specific issues requiring input and this is a very individual factor. Average time on BSC for this group can also be very variable and I do not think its possible to give an accurate frame for this - but probably around 3-6 months.				
6	Radiological progression does not necessarily correlate with survival for patients treated with Tebentafasup. Therefore formally moving onto BSC (and involvement of the Palliative Care Team) requires case-by-case assessment and is unlikely to be suitable for everyone. If a patient is clinically well, tolerating treatment and has no significant cancer-related symptoms then even with progression on scan, they are more likely to continue under the care of the Oncology Team and remain on Tebentafusp. If a patient is progressing clinically or symptomatically, then they would move onto BSC and this is likely to be needed for 3-6 months usually.				

7	This and the previous question makes be wonder whether you mean something other than literal Best Supportive Care.
8	Yes, at least a proportion of this sub-population would receive BSC after progression. From experience the sub-population of longer-term survivors would however receive BSC at a later time point following disease progression, as it is more likely for them to remain asymptomatic, or minimally symptomatic, with preserved quality of life, for a longer period of time. A small proportion may not require BSC. I do not feel able to put an average time on this, given the small patient numbers.
9	Yes- an offer of BSC forms background support for all patients including long term survivors but the degree of support required may be minimal until the more advanced symptomatic stage which may be a short number of years after progression
10	The answer is Yes, and all patients start on BSC after the progression. In my experience these patients access these services when they are clinically deteriorating . On average they receive BSC for the final 3-4 months of their lives.
11	These are rare patients. The fact that they have progressed brings with it much angst and few patients are symptom-free, to they will likely be referred for BSC alongside also maintaining their secondary care team links
12	The answer is as for 1 above. Patients with progressive disease will have ongoing review. Some will be asymptomatic for a period of time, others will have symptoms, but they will have regular review.

Question 3					
3. Would the rest of the population (i.e. non-long-term survivors) receive BSC after progression? If yes, how long after progression would they begin receiving BSC and on average, how long for? Please provide your answer along with relevant justification.					
Expert	**Response**				
1	yes probably 6-12 months				
2	Yes, see answer above				
3	Yes around 6 months				
4	BSC in the face of symptomatic progression is generally required for a short period time perhaps weeks to short months prior to death.				
5	This population tend to have more rapidly progressive disease - start BSC at the point of progression often and are using the resources for around 3 months on average.				
6	Patients with confirmed progression with no options for treatment of their ocular melanoma would move onto BSC. I would usually arrange this at the point at which progression is confirmed, if I had not arranged it in advance. On average they are likely to receive this for 3-6 months but there is significant variability.				
7	Sorry, makes no sense.				
8	Yes, the non-long term survivors would receive BSC after progression. By definition, if survival is shorter, the disease is likely to behave more aggressively and therefore result in clinical symptoms and an associated deterioration in quality of life much sooner. It is difficult to be precise regarding when BSC would be required, but it is likely to be within days to weeks of disease progression and continue for a short number of months (2-4).				

9	Yes. BSC initiated at the point of progression and duration would be for the anticipated life expectancy (median 9-12 months)
10	Yes they will, and these patients will be started on BSC on noticing radiological progression. At this point, some of these patients already show clinical signs of disease progression and more likely to receive BSC almost immediately. Rest of the cases start to deteriorate in few weeks, after the radiological progression is noticed and to start using the services. These patients usually receive BSC for around 2-3 months.
11	Yes - immediately and might be 3-4 months on average.
12	Yes, as for above.

APPENDIX 6: OVERALL SURVIVAL (APRIL 2024 DATA CUT) FOR INTENTION TO TREAT POPULATION



Evidence dossier

Expert elicitation in response to an upheld appeal (NICE technology appraisal ID1441, tebentafusp for advanced uveal melanoma)

Contents

Note: all information provided is sourced using the original Company Submission for ID1441.[1] Relevant additional articles (see Section 5) were identified by stakeholders and the elicitation project team. All material marked in yellow is 'academic in confidence'.

Abbreviations

ACM	Appraisal committee meeting
DCO	Data cut-off
ITT	Intention to treat
HLA	Human leukocyte antigen
PCP	Pre-choice pembrolizumab subgroup
PFS	Progression-free survival
OS	Overall survival
UM	Uveal melanoma
TTD	Time to treatment discontinuation

1 Technology appraisal (ID1441) overview

1.1 Prevalence of uveal melanoma in the UK

- The proposed intervention, tebentafusp, is indicated for the treatment of patients with advanced (unresectable or metastatic) UM who are HLA-A*02:01 positive.
- The HLA-A*02:01 positive mutation is present in approximately 47% of the population and it is estimated that approximately 100 patients per year will be eligible for the use of tebentafusp.

1.2 Target population

- The subgroup of patients who were pre-selected to receive pembrolizumab. This subgroup is termed as the pre-choice pembrolizumab subgroup (PCP subgroup).
    - At ACM1, it was concluded that pembrolizumab should be the key comparator in this appraisal.
    - The subgroup of patients who were pre-selected to receive pembrolizumab was the population of interest. The two arms within this subgroup are referred to as tebentafusp-PCP and pembrolizumab. This subgroup composed ~80% of the original population.
    - Note: randomisation was preserved as patients who were allocated pembrolizumab (in a scenario where tebentafusp was not available) were subsequently randomised for treatment with tebentafusp or pembrolizumab.
    - For further details on the target population relevant to ID1441 see the supporting information in Section 5.1, eligibility criteria in Section 6.1 and the publicly available project documents on the NICE project page.
    - Assessments of demographic and baseline characteristics are presented in Section 6.2.

1.3 Proposed intervention – tebentafusp

- Tebentafusp is a novel immunotherapy and described as an Immune Mobilising Monoclonal T cell receptor Against Cancer (ImmTAC®) drug.
- The drug is a systemic treatment designed specifically for patients who are HLA-A*02:01-positive. Tebentafusp directly targets uveal melanoma cells that express gp100 protein presented by HLA-A*02:01 and recruits T-cells (and other immune-associated cells) to destroy the UM cells.
- For further details of tebentafusp and the mechanism of action, please refer to the articles included in the appendix.

1.4 Pivotal trial

- The pivotal trial was the open-label, phase 3 randomised controlled trial, IMCgp100-202. More information on the pivotal trial and supporting trials can be found in Section 5.1.

  - Treatment with tebentafusp was allowed beyond initial radiological progression (according to specific criteria) and cross-over was later permitted from the comparator arm to tebentafusp following a protocol amendment. After the protocol amendment, 16 patients (14 from the PCP subgroup) received tebentafusp post-progression from the comparator arm according to the 'cross-over' criteria. An additional 8 patients from the PCP subgroup received tebentafusp post-progression that did not fulfil the 'cross-over' criteria. Hence, 22 (21%) of the 103 patients from the PCP subgroup received tebentafusp post-progression after the primary analysis and would likely have a significant confounding effect on the OS estimates for subsequent data cuts after the primary analysis.
- Treatment administration for tebentafusp and pembrolizumab is included in Section 6.3. For further details of the phase 3 and phase 1/2 trials using tebentafusp in advanced UM, please see the included publications in Section 5.1.

1.5 Technology appraisal ID1441 background

- Two NICE appraisal committee meetings (ACMs) were held to discuss ID1441. The draft final appraisal decision was that tebentafusp was not deemed to be cost-effective and would not be recommended for the Cancer Drugs Fund.
- This decision was appealed by the Company (Immunocore) and the two relevant patient groups. The upheld appeal points relevant to this elicitation workshop relate to the un-addressed high level of uncertainty in the choice of overall survival (OS) model extrapolation.

2 Quantities of interest

During this elicitation workshop, the primary aim is to elicit the long-term overall survival when treating advanced/metastatic UM with tebentafusp and pembrolizumab, with associated uncertainty at key timepoints for the PCP subgroup population of the IMCgp100-202 trial.

3 Evidence summary

To make the judgements on long-term survival, data from the pivotal trial (IMCgp100-202) using the most recent data cut-off (DCO) (June 2023) are presented, Section 4.

Supporting documents including earlier data from IMCgp100-202 and earlier phase trials for tebentafusp and external evidence on the survival when treating with other interventions are included in Section 5.

Given that tebentafusp is a comparatively new treatment, we have also included more detailed background of the trial eligibility criteria, population baseline characteristics, treatment administration and additional progression-free survival (PFS) and time to treatment discontinuation (TTD) data in Appendix A. Further general information regarding the mechanism of action of tebentafusp is included in Appendix B.

4 Survival data: IMCgp100-202 trial PCP subgroup

The Kaplan-Meier curve, using the June DCO, for overall survival in the PCP subgroup is shown in Figure 1. Supporting PFS and TTD Kaplan-Meier curves are presented in Section 6.4 and 6.5 respectively. Note that for PFS, the data are presented for the ITT group using

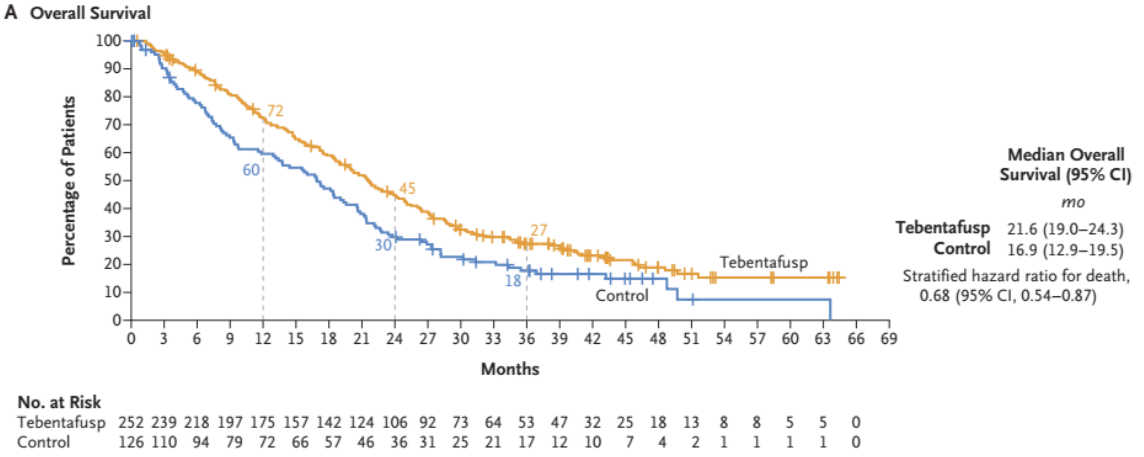
the August 2021 DCO, and for TTD the data are presented for the PCP subgroup using the April 2022 DCO.

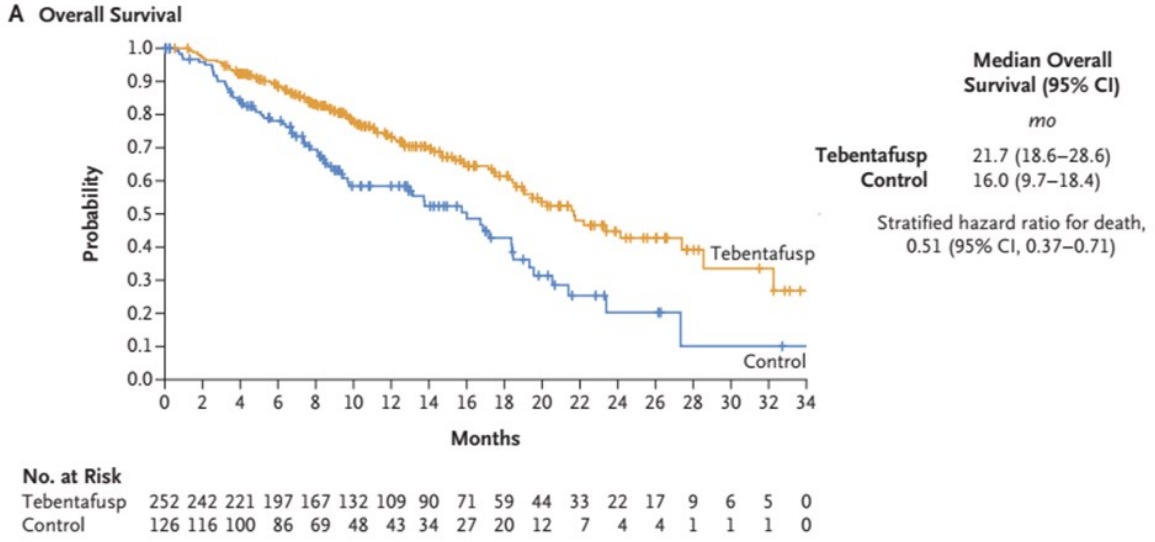
Figure 1: Kaplan-Meier estimate of overall survival for study IMCgp100-202 using the June 2023 data cut-off. There is relatively high censoring toward the end of the Kaplan-Meier. Also note that there is some cross-over from the pembrolizumab arm to the tebentafusp arm, as outlined in Section 1.3.

[redacted]

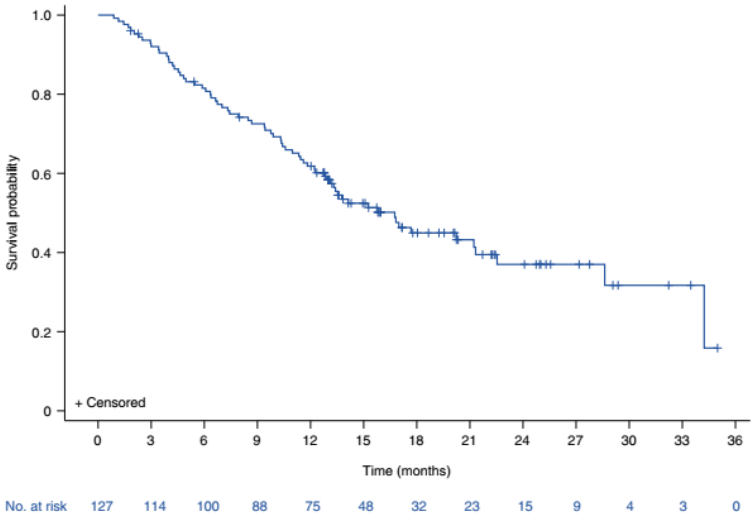
5 Supporting information

5.1 Trial evidence

IMCgp100-202 ITT (latest data cut-off June 2023)		
Resource	Description	Link to document
Hassel *et al.* 2023[2]	Three-Year Overall Survival with Tebentafusp in Metastatic Uveal Melanoma • Most-recent publication of the IMCgp100-202 trial, includes 3-year OS for ITT population. • Population is systemic treatment-naïve. • Safety results/assessment presented. • Supports long-term efficacy of tebentafusp.	
		
IMCgp100-202 ITT (earlier data cut-off) and earlier trials		
Resource	Description	Link to document
Nathan *et al.* 2021[3]	Overall Survival Benefit with Tebentafusp in Metastatic Uveal Melanoma • Primary phase 3 clinical trial results displaying OS benefit for the ITT group. • Population is systemic treatment-naïve. • Survival at 1 year reached, 73% in tebentafusp and 59% in control group.	



Carvajal *et al.* 2022[4]	Clinical and molecular response to tebentafusp in previously treated patients with metastatic uveal melanoma: a phase 2 trial • Multi-center, phase 1/2 single arm study of tebentafusp. • Primary endpoint was objective response rate based on RECIST criteria. • Discussion of adverse effects and toxicity, low overall response rate, and improvement in OS.	



5.2 External evidence

Meta-analysis		
Resource	Description	Link to document
Rantala *et al.* 2019[5]	Overall survival after treatment for metastatic uveal melanoma: a systematic review and meta-analysis • Meta-analysis to advance interpretation of OS as an outcome. • Systematic review and meta-analysis using patient level data.	

	• Multiple modalities of treatment and compared to reference modality – chemotherapy. Modalities included – chemotherapy, chemoimmunotherapy, hepatic intra-arterial chemotherapy, transarterial chemoembolization, isolated hepatic perfusion, check-point inhibitors, protein kinase inhibitors, selective internal radiation therapy, immunoembolization, immunosuppressant, liver-directed thermotherapy, vaccine, surgery.	
Khoja *et al.* 2019[6]	Meta-analysis in metastatic uveal melanoma to determine progression free and overall survival benchmarks: an international rare cancers initiative (IRCI) ocular melanoma study • Meta-analysis using patient level data to help determine benchmarks of PFS and OS. • Study of covariates associated with shorter PFS. Multiple types of treatments included - anti-angiogenic, chemotherapy, immunotherapy, kinases, liver directed.	
Data for tebentafusp and other interventions		
Resource	Description	Link to document
Petzold *et al.* 2023[7]	Is tebentafusp superior to combined immune checkpoint blockade and other systemic treatments in metastatic uveal melanoma? A comparative efficacy analysis with population adjustment • Indirect comparisons of tebentafusp OS and PFS with combined immune checkpoint blockade therapies. • Shows benefit in OS when treating with tebentafusp	

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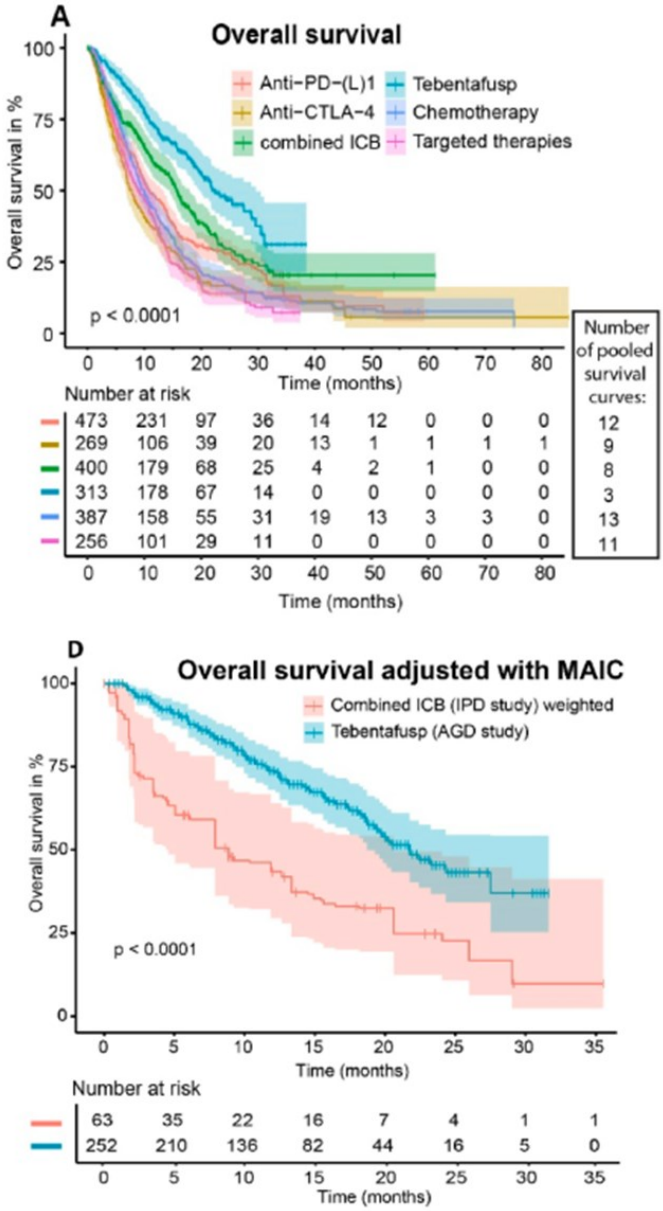
<td colspan="3"> 
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<td>Piulats et al. 2024[8]</td>
<td>Overall survival from tebentafusp versus nivolumab plus ipilimumab in first-line metastatic uveal melanoma: a propensity score-weighted analysis
• Uses propensity scoring methods to compare tebentafusp or pembrolizumab with nivolumab plus ipilimumab.
• Shows benefit in OS when treating with tebentafusp.</td>
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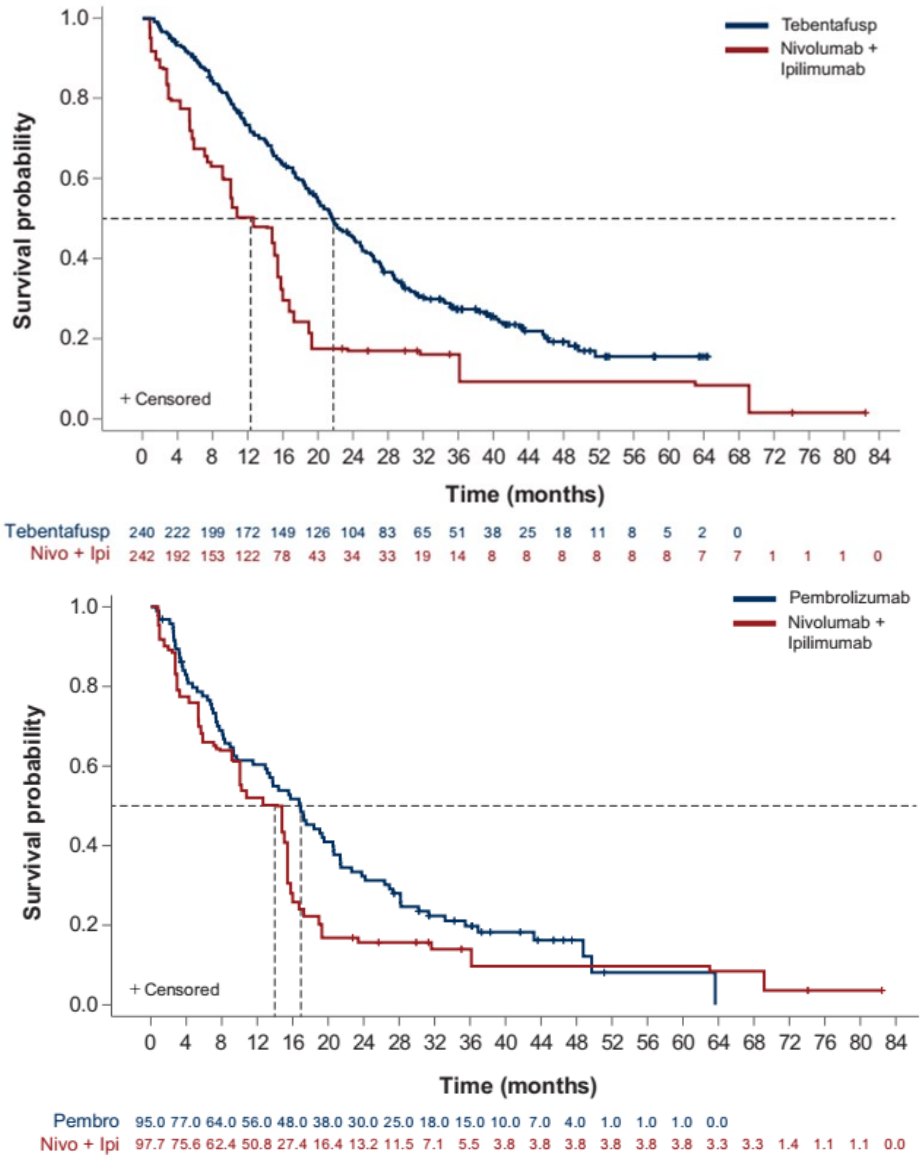

Orloff *et al. 2023*[9]	Effect of subsequent therapies including checkpoint inhibitors on overall survival in a phase III randomized trial of tebentafusp in first-line metastatic uveal melanoma: Long-term follow-up • Conference abstract outlining the statistical assessment of subsequent therapies. • OS benefit of tebentafusp was shown to be due to tebentafusp **not** due to subsequent therapies.	
Data for other interventions		
Resource	Description	Link to document
Wolchok *et al.* 2022[10]	Long-Term Outcomes With Nivolumab Plus Ipilimumab or Nivolumab Alone Versus Ipilimumab in Patients With Advanced Melanoma • 6.5-year efficacy report of nivolumab + ipilimumab and nivolumab alone versus ipilimumab. • Data from the phase 3 CheckMate 067 trial.	

Piulats *et al.* 2021[11]	Nivolumab Plus Ipilimumab for Treatment-Naïve Metastatic Uveal Melanoma: An Open-Label, Multicenter, Phase II Trial by the Spanish Multidisciplinary Melanoma Group (GEM-1402) • Presents the efficacy of nivolumab + ipilimumab as a first line therapy with respect to the 12-month OS. • Target population includes patients who are not eligible for liver resection. • Modest improvement in OS shown over historical	
Rantala *et al.* 2020[12]	Metastatic uveal melanoma managed with best supportive care • Retrospective cohort study assessing population-based OS. • Eligible patients had previously validated prognostic stages of advanced UM patients who had not been treated for advanced UM prior to receiving BSC. • Provides historical data for comparisons to actively treated patients.	
Bol *et al.* 2019[13]	Real-World Impact of Immune Checkpoint Inhibitors in Metastatic Uveal Melanoma • Analysis of survival before and after the first approval of immune checkpoint inhibitors for the treatment of metastatic UM. • Partial response to first-line treatment was observed, plus an improvement in median OS.	
Heppt *et al.* 2019[14]	Combined immune checkpoint blockade for metastatic uveal melanoma: a retrospective, multi-center study • Assessment of combined checkpoint blockade therapy with respect to PFS and OS and response rates.	
Rossi *et al.* 2019[15]	Pembrolizumab as first-line treatment for metastatic uveal melanoma • Prospective observational cohort single arm study. • Investigation of efficacy and safety of pembrolizumab as first-line therapy. • Median OS not reached. • Pembrolizumab is not significantly different compared to other treatments. • For responding patients, pembrolizumab does provide good disease control.	

Schadendorf *et al.* 2015[16]	Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma • Pooled analysis of OS from 10 prospective and 2 retrospective studies of ipilimumab for advanced melanoma. • At the time, this was the largest analysis of OS for ipilimumab treated advanced melanoma patients. • Showed potential plateau in survival curve at approximately 3 years. • Only 3/12 studies were exclusively treatment naïve patients, and uveal melanoma patients were only included in the expanded access programme which was not included in the main analysis.	

6 Appendix A: IMCgp100-202 trial information

6.1 Eligibility criteria

6.1.1 Inclusion criteria

1. Male or female patients aged ⩾18 years of age at the time of informed consent
2. Ability to provide and understand written informed consent prior to any study procedures
3. Histologically or cytologically confirmed metastatic UM
4. Had to meet the following criteria related to prior treatment:
   - No prior systemic therapy in the metastatic or advanced setting including chemotherapy, immunotherapy, or targeted therapy
   - No prior regional liver-directed therapy, including chemotherapy, radiotherapy, or embolisation
   - Prior surgical resection of oligometastatic disease was allowed
   - Prior neoadjuvant or adjuvant therapy was allowed provided administered in the curative setting in patients with localised disease. Patients must not have been retreated with an investigator's choice therapy that was administered as adjuvant or neoadjuvant treatment. Additionally, patients who received nivolumab as prior adjuvant/neoadjuvant treatment should not have received pembrolizumab as investigator's choice therapy
5. HLA-A*02:01 positive by central assay
6. Life expectancy of > 3 months as estimated by the investigator
7. ECOG performance status score of 0 or 1 at screening
8. Patients had measurable or non-measurable disease according to RECIST v1.1
9. All other relevant medical conditions had to be well-managed and stable, in the opinion of the investigator, for at least 28 days prior to first administration of study drug

6.1.2 Exclusion criteria

Patient with any out-of-range laboratory values defined as:

1. Serum creatinine >1.5 × ULN and/or creatinine clearance <50 mL/minute
2. Total bilirubin >1.5 × ULN, except for patients with Gilbert's syndrome, who were excluded if total bilirubin >3.0 × ULN or direct bilirubin >1.5 × ULN
3. Alanine aminotransferase >3 × ULN
4. Aspartate aminotransferase >3 × ULN
5. Absolute neutrophil count <1.0 × 109/L
6. Absolute lymphocyte count <0.5 × 109/L
7. Platelet count <75 × 109/L
8. Hemoglobin <8 g/dL
9. History of severe hypersensitivity reactions (e.g., anaphylaxis) to other biologic drugs or monoclonal antibodies
10. Clinically significant cardiac disease or impaired cardiac function

6.2 Population baseline characteristics

6.2.1 Intention to treat (ITT)

Baseline characteristics according to tebentafusp and investigator's choice were reported in Nathan et al..[3] Among all the patients who had undergone randomization, 36% had an LDH level above the ULN, 5% had extrahepatic disease only, and the median time since the primary diagnosis was 2.8 years, with no substantial difference between the groups in any of these variables.[3]

Table 1: Demographic and disease characteristics at baseline (ITT population) reproduced from Nathan et al. 2021.

Characteristic	Tebentafusp Group (N=252)	Control Group (N=126)
Median age (range) — yr	64 (23–92)	66 (25–88)
Male sex — no. (%)	128 (51)	62 (49)
Median time since primary diagnosis (range) — yr	3.0 (0.1–25)	2.4 (0.1–36)
ECOG performance-status score — no. (%)†		
0	192 (76)	85 (67)
1	49 (19)	31 (25)
2	0	1 (1)
Data missing	11 (4)	9 (7)
Lactate dehydrogenase >ULN — no. (%)	90 (36)	46 (37)
Largest metastatic lesion — no. (%)‡		
≤3.0 cm, stage M1a	139 (55)	70 (56)
3.1 to 8.0 cm, stage M1b	92 (37)	46 (37)
≥8.1 cm, stage M1c	21 (8)	10 (8)
Location of metastasis — no. (%)		
Hepatic only	131 (52)	59 (47)
Extrahepatic only	9 (4)	10 (8)
Hepatic and extrahepatic	111 (44)	55 (44)
Data missing	1 (<1)	2 (2)
Previous surgical therapy for metastatic disease — no. (%)	24 (10)	9 (7)

* ULN denotes the upper limit of the normal range. Percentages may not sum to 100 because of rounding.
† The Eastern Cooperative Oncology Group (ECOG) performance-status scale ranges from 0 to 5, with higher scores indicating greater disability; a score of 0 indicates no symptoms, 1 mild symptoms, and 2 moderate symptoms.
‡ Lesions were assessed with the use of the seventh edition of the Cancer Staging Manual of the American Joint Committee on Cancer.

6.2.2 Stratified by pre-choice of therapy in the ITT population

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. The inverse was evident for patients preselected for ipilimumab. A similar pattern was also evident for tumour size. In summary, the prognostic variables for patients preselected for dacarbazine or ipilimumab was different to patients pre-selected for pembrolizumab prior to randomization.[1]

Table 2: Summary of baseline disease characteristics by investigator pre-choice of therapy in the ITT population 04 April 20220 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]

	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]
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]

6.3 Treatment administration

6.3.1 Tebentafusp

Tebentafusp was administered by IV transfusion following the intra-patient escalation regimen. Patients received 20 µg on C1D1, 30 µg on C1D8, and an escalated dose of 68 µg on C1D15 and weekly thereafter. Due to the anticipated cytokine release-associated toxicity with tebentafusp following the first three doses, patients were monitored for at least 16 hours after dosing as an inpatient following the weekly doses on C1D1, C1D8, and C1D15. Use of prophylactic steroids was not mandated.

6.3.2 Pembrolizumab

Pembrolizumab at the dosing regimen of 2 mg/kg up to a maximum of 200 mg or 200 mg administered IV were approved locally given on Day 1 of each 21-day cycle. No extended monitoring after dosing was required.

6.4 Progression-free survival (PFS)

Figure 2: Kaplan-Meier curve for PFS ITT group using DCO August 2021.

6.5 Time to treatment discontinuation (TTD)

Figure 3: Kaplan-Meier estimate of TTD for study IMCgp100-202 PCP analysis using DCO 04 April 2022.

7 Appendix B: General background of tebentafusp and mechanism of action

Resource	Description	Link to document
Howlett *et al.* 2023[17]	Tebentafusp: a first-in-class treatment for metastatic uveal melanoma • Review article which focusses on the clinical development of tebentafusp, the mechanism of action and the resultant evolution of the management of advanced UM.	
Damato *et al.* 2019[18]	Tebentafusp: T Cell Redirection for the Treatment of Metastatic Uveal Melanoma • Overview of UM biology, the metastatic disease, overview of immunotherapy and the general mechanisms of action. • Review of tebentafusp in clinical studies with OS curves from earlier phase clinical studies.	
Wang et al. 2023[19]	Tebentafusp: a novel drug for the treatment of metastatic uveal melanoma • Review that summarises the pharmacodynamic and pharmacokinetic profile, and the clinical trials that have already been conducted to assess tebentafusp efficacy.	
Jager *et al.* 2020[20]	Nature Primer: Uveal melanoma • Detailed description and review of uveal melanoma including primary disease and advanced/metastatic disease.	

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Face-to-Face Workshop Report

Expert elicitation in response to an upheld appeal (NICE technology appraisal ID1441, tebentafusp for advanced uveal melanoma)

REPORT BY THE DECISION SUPPORT UNIT

May 2024

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ABOUT THE DECISION SUPPORT UNIT

The Decision Support Unit (DSU) is based at the University of Sheffield with members at the Universities of York, Bristol, Leicester, Warwick and the London School of Hygiene and Tropical Medicine. The DSU is commissioned by The National Institute for Health and Care Excellence (NICE) to provide a research and training resource to support the Institute's Centre for Health Technology Evaluation Programmes. Please see our website for further information: nicedsu.org.uk

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Ren, S., Forsyth J., Gosling, JP, Latimer, N., Oakley, J., Rutherford, M., Uttley, L., Wilson, K. Face-to-Face Workshop Report. Expert elicitation in response to an upheld appeal (NICE technology appraisal ID1441, tebentafusp for advanced uveal melanoma). 2024. Available at nicedsu.org.uk.

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ABBREVIATIONS

ACM	Appraisal committee meeting
CM	Cutaneous melanoma
DCO	Data cut-off
EAP	Expanded access programme
ITT	Intention to treat
HLA	Human leukocyte antigen
PCP	Pre-choice pembrolizumab
PFS	Progression-free survival
OS	Overall survival
RIO	Rational Impartial Observer
UM	Uveal melanoma
QoI	Quantity of Interest
TA	Technology appraisal
TTD	Time to treatment discontinuation

1. BACKGOUND

Two NICE appraisal committee meetings (ACMs) were held to discuss NICE single technology appraisal (TA) ID1441, tebentafusp for advanced uveal melanoma.[1] The draft final appraisal decision was that tebentafusp was not deemed to be cost-effective and would not be recommended for the Cancer Drugs Fund.[1]

An appeal hearing was held on 20 October 2023, which was upheld on several points. All of the upheld points related to the appeal panel's expectation that, faced with significant uncertainty, the input of experts should be particularly important in informing the committee's judgements.

The aim of the elicitation workshop is to address one of the upheld appeal points relating to the long-term overall survival (OS).

2. WORKSHOP INFORMATION

Date	23 April 2024
Format	Face-to-face (10:00-15:15 including 1.5 hours training)
Expert participants*	Dr Clare Barlow (Somerset Foundation Trust) Dr Steve Nicholson (Mid & South Essex NHS Foundation Trust) Dr Miranda Payne (Oxford University Hospitals NHS Foundation Trust) Dr Rachel Plant (University Hospital Dorset) Dr Dulani Ranatunge (Queens Center for Oncology, Hull University Teaching Hospital)
Chair	Dr Kate (Shijie) Ren (University of Sheffield)
Facilitator	Professor Jeremy Oakley (University of Sheffield)
Recorder	Dr Jessica Forsyth (University of Sheffield)
Quantity of Interest (QoI)	**QoI 1** For the pre-choice pembrolizumab (PCP) subgroup population from the IMCgp100-202 trial in **the tebentafusp arm**, the proportion of patients, expressed as a number per 1000, who are still alive at year 8 after randomisation. **QoI 2** For the pre-choice pembrolizumab (PCP) subgroup population from the IMCgp100-202 trial in **the pembrolizumab arm (excluding effect of tebentafusp as a subsequent treatment)**, the proportion of patients, expressed as a number per 1000, who are still alive at year 8 after randomisation.
Elicitation protocol	The Sheffield Elicitation Framework (SHELF)[2]

* Note: expertise and declaration of conflicts of interest are presented in Appendix 1.

3. MOTIVATION AND TRAINING

Experts were given a presentation on the background of the project and the motivation for using probability distributions to represent uncertainty. Experts received training on general probability elicitation, biases in probability judgements, and survival extrapolation including survivor and hazard functions and their qualitative interpretation. A practice exercise on eliciting long-term survival data for lung cancer patients who quit smoking was carried out.

4. EVIDENCE

An Evidence Dossier was compiled,[3] which included the following data from the IMCgp100-202 trial for both the tebentafusp and pembrolizumab arm:

- Baseline characteristics
- OS for the PCP subgroup (June 2023)
- Time to treatment discontinuation (TTD) for the PCP subgroup (April 2022)
- Progression-free survival (PFS) for the intention to treat (ITT) group (August 2021)

The Evidence Dossier also included the following supporting documents:

- IMCgp100-202 trial evidence
    - Hassel *et al.* 2023[4]
    - Nathan *et al.* 2021[5]
- IMCgp100-102 trial evidence
    - Carvajal *et al.* 2022[6]
- External evidence
    - Meta-analysis: Rantala *et al.* 2019[7], Khoja *et al.* 2019[8]
    - Data for tebentafusp: Petzold *et al.* 2023[9], Piulats *et al.* 2023[10], Orloff *et al. 2023*[11]
    - Data for other interventions: Wolchok *et al.* 2022[12], Piulats *et al.* 2021[13], Rantala *et al.* 2020[14], Bol *et al.* 2019[15], Heppt *et al.* 2019[16], Rossi *et al.* 2019[17], Schadendorf *et al.* 2015[18]

Following clarification recommendations from the online workshop,[19] information regarding patient transfer onto the expanded access program (EAP)/commercial product was presented to the experts. The company's response to the clarification question can be found in Appendix 2: Company response to EAP/commercial product queries and is summarised below.

- Patients were censored for analysis of treatment discontinuation when the study was closed, i.e. censored when they were switched to either commercial product or the EAP.
- Patients continued to be followed up for OS. OS data for patients in Germany were lost to follow up due to 'sponsor ended study' and were censored for the analysis of OS at the time the study closed. The time points for censoring of OS for the 12 patients from the tebentafusp arm were between 27.5 and 49 months.

The experts sought clarification on the subsequent treatments received by patients after discontinuation of tebentafusp or pembrolizumab and stated that this was not presented in the Evidence Dossier and should be highlighted in subsequent reports.

The elicitation team advised that patients were able to receive subsequent treatments following tebentafusp or pembrolizumab and re-iterated that the effect of subsequent treatments (excluding subsequent treatment with tebentafusp in the pembrolizumab arm) should be considered when making judgements. The Facilitator and Chair stated that this would be clarified with the company for inclusion within the workshop report. The experts agreed to base their judgements based on this principle. After the workshop, the elicitation team clarified with the company the details of the subsequent treatment received in the trial, the company response is included in Appendix 3: Company response to subsequent treatments queries.

Additionally, the experts sought clarification on the data included within the meta-analysis published by Rantala *et al.*[7] which was agreed at NICE ACM1 to be the lower benchmark of OS for potential comparator therapies. The experts discussed that the data used by Rantala *et al.* included multiple therapy options and included data from older studies as well as more recent sources. To further clarify the data presented from the Rantala *et al.* meta-analysis, the elicitation team also confirmed that the Rantala *et al.* data corresponded to data for first-line therapies only.

5. QUANTITY OF INTEREST 1

The first quantity of interest (QoI 1) was defined as: for the PCP subgroup population from the IMCgp100-202 trial in **the tebentafusp arm**, the proportion of patients, expressed as a number per 1000, who would still be alive at year 8 after randomisation.

5.1 Individual judgements

The Facilitator asked the experts to provide their judgments for the lower plausible limit, upper plausible limit, median, lower quartile (Q1), and upper quartile (Q3). The experts were asked to make their judgements independently, without conferring.

Table 1 shows the experts' individual judgements for QoI 1.

Table 1: Experts' individual judgements for QoI 1

Expert	Lower plausible limit	Lower quartile	Median	Upper quartile	Upper plausible limit
G	10	50	70	110	200
H	20	40	60	85	120
I	30	130	160	180	220
J	100	125	150	175	250
K	20	65	95	120	180

Abbreviations: QoI, quantity of interest.

5.2 Scenario testing

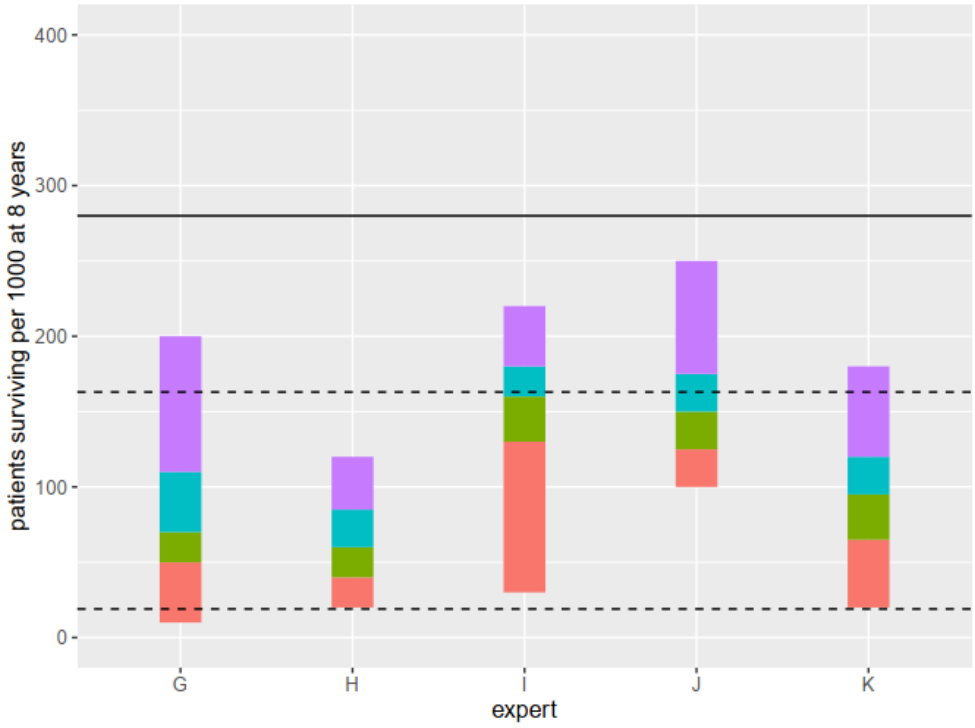
After the experts' individual judgements had been recorded, the experts were then presented with an extrapolation based on a particular scenario. It was explained to the experts that the aim of presenting the scenario was to give a point of reference for reflection on their individual

judgements: no claims were made by the elicitation team regarding the probability of the scenario being true.

The scenario was that the hazard remained unchanged from year 3 onwards. An exponential model was fitted to the 3-4 years survival data and extrapolated to 8 years. Based on this, an approximate 95% credible interval was reported for the survival at 8 years, to indicate what range of values would be statistically consistent with the assumption of no change in the hazard. The experts were invited to reflect on whether their plausible ranges exceeded either interval limit, and this provided a starting point for the group discussion. The experts' judgements and the 95% credible interval corresponding to the constant hazard scenario are shown in

Figure 1.

Figure 1: Individual quartile judgements for QoI 1
(For each expert, each coloured section represents a range judged to contain the true QoI with probability 25%. Values outside the range indicated by the four coloured sections were not judged to be plausible. The solid line is the upper Kaplan-Meier 97.5% confidence limit for survival at 4 years. The dashed lines show an approximate 95% credible interval for survival at 8 years that is statistically consistent with a scenario of no change in hazard from year 3 onwards.)



Abbreviations: QoI, quantity of interest.

5.3 Group discussion

A facilitated group discussion between the experts followed.

The Facilitator invited the experts to discuss the potential factors that could contribute to increasing and decreasing hazards.

Regarding the potential for decreasing hazards, the experts thought that the risk of death would be highest in the first two years of the study, with a decrease in hazard after that. Both arms are heterogeneous, and experts believed there would be a cohort of longer-term survivors whose biology of disease predisposes them to increased survival times regardless of treatment received. Clinical visit frequency would be reduced for longer-term survivors, with reduced frequency of radiological assessments due to associated lower risk.

The experts commented that they have observed patients treated with tebentafusp who had progressed radiologically, but clinically were doing very well. The experts also commented that PFS based on RECIST v1.1. criteria for this disease appears to be a poor predictor of OS, further supporting that often patients have good performance levels even at progression. The experts then discussed that they currently do not understand why this is happening, but this could potentially be evidence that the disease biology is being altered by the treatment.

One expert suggested that the effect of trial enrolment and increased monitoring due to the trial design could result in a decreasing hazard. Other experts expected this effect to be relevant at trial initiation, but less so later in the trial.

The Facilitator invited the experts to discuss cure plausibility. The experts were unanimously hesitant to state that a cure is possible in the tebentafusp arm, noting the difficulty in assessing potential cure due to the novel action of tebentafusp and lack of data. They did believe, however, that there is likely to be a longer-term surviving subgroup of patients who experience good disease control even at later time points.

The experts did not think there was a good case to be made for increasing hazards, beyond the usual effects of aging and medical comorbidities.

5.4 Reflection after discussion

The experts were each asked to reflect on the discussion that had taken place thus far, and comment on whether they had changed their position from their initial judgements.

G: stated that they would increase their estimates to reflect the points raised in the group discussion. This amendment largely related to the presence of longer-term survivors and uncertainty due to the novel method of action of tebentafusp.

H: believed that they would increase their upper plausible limit due to the presence of longer-term survivors but stated that they would not increase their estimate as high as expert J due to consideration of aging and patient comorbidities.

I: discussed potential uncertainty in their lower plausible limit and stated that they would potentially amend their initial judgement by increasing their estimate due to the presence of longer-term survivors. Like expert H, the expert believed that age and patient comorbidities would influence survival at 8 years and did not wish to amend their estimates to values as high as those predicted by expert J.

J: expressed overall confidence in their estimates, judging it implausible that survival would be below 10% at 8 years, and was therefore reluctant to change any of their individual judgements.

K: discussed their uncertainty in the judgements due to the novel method of action and limited data available. Discussed the potential to slightly increase estimates to reflect the presence of longer-term survivors.

5.5 RIO judgements and distribution

The experts were then asked to consider a single set of probability judgements that would appropriately represent the views and evidence presented. Specifically, they were asked to propose a set of probabilities from the perspective of a "Rational Impartial Observer" (RIO): an individual who has listened to all the discussion and seen all the evidence and would impartially consider their own uncertainty based on this. It was explained that "RIO's distribution" would be presented as the conclusion from the workshop, but that any dissenting views of individual experts would be noted.

The Facilitator asked the experts what RIO would believe to be the chance of survival being less than 100 per 1000 at 8 years post-randomisation. The experts discussed the potential for longer-term survivors and suggested probabilities in the range 15% to 20%.

The Facilitator asked the experts what RIO would believe to be the chance of survival being greater than 200 per 1000 at 8 years post-randomisation. The experts discussed the credible intervals of the overall survival at 4 years post-randomisation, that survival rates this high at 8 years could imply that very few patients die between 4 and 8 years and whether this is representative of what is occurring within this patient group. Probabilities in the range 5% to 10% were suggested.

The Facilitator asked the experts what RIO would believe to be the chance of survival being greater than 150 per 1000 at 8 years post-randomisation. The experts suggested a probability of 50%.

The Facilitator fitted a Beta distribution to the following RIO probabilities using the SHELF R package[20]

- 15% probability that survival is below 100 per 1000
- 50% probability that survival is greater than 150 per 1000
- 10% probability that survival is greater than 200 per 1000

This resulted in a Beta(9.7, 54.8) distribution for the QoI, which was presented to the experts. This distribution implied a 99% probability the survival would be above 64 per 1000. The Facilitator questioned whether RIO could be this certain of the survival exceeding this value noting the initial judgements of some experts.

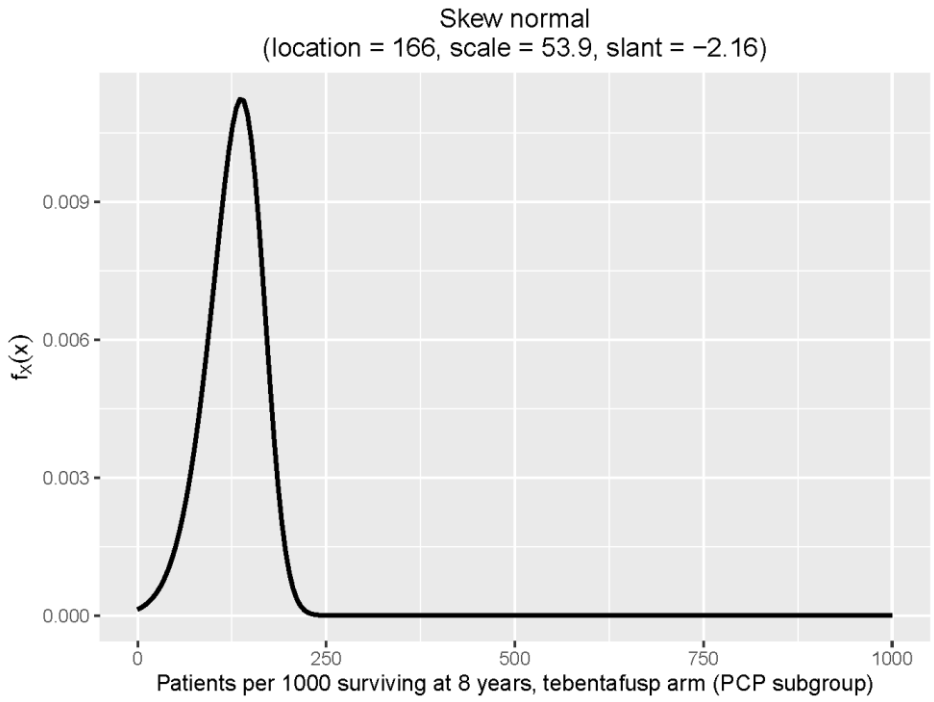
One expert believed that based on the group discussion 64 was too high for a 1st percentile and also suggested that the median should be reduced. Regarding the first RIO judgement, there was consensus around a stronger case for a decreasing hazard to be reflected in the RIO distribution, but uncertainty about when a 'flattening' of the survival curve might occur, and how it might compare with baseline mortality if tebentafusp was not curative.

Revised RIO judgements were considered,

- 5% probability that survival is below 60 per 1000,
- 50% probability that survival is greater than 130 per 1000,
- 1% probability that survival is greater than 200 per 1000,

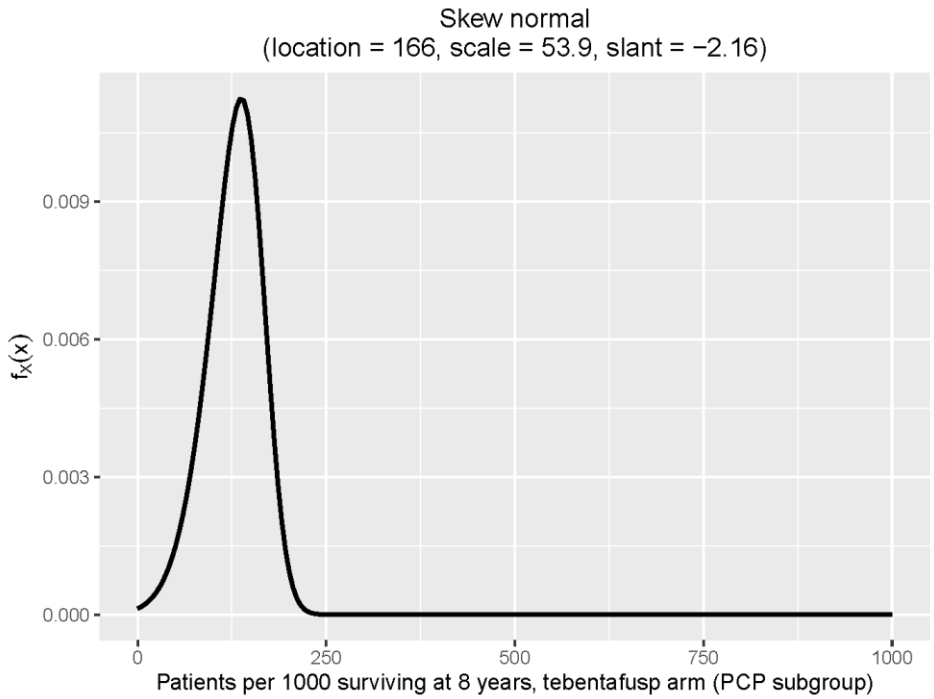
and a skew normal distribution was fitted and shown to the experts (See

Figure 2: The final chosen RIO distribution for QoI 1



). The percentiles from the fitted RIO distribution are presented in

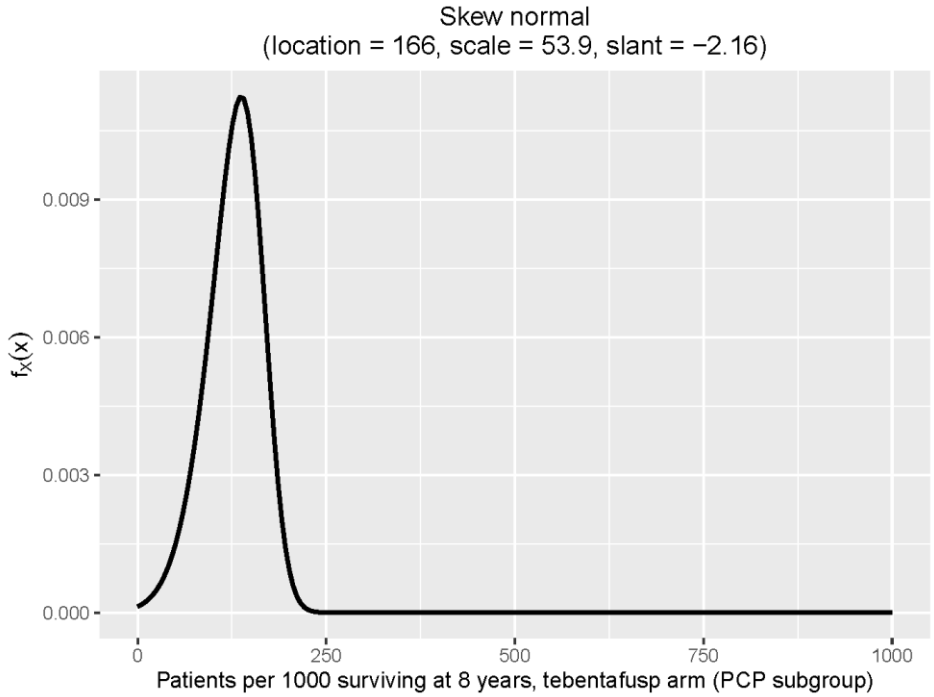
Figure 2: The final chosen RIO distribution for QoI 1



Abbreviations: RIO, Rational Impartial Observer; QoI, quantity of interest.

Table 2. This was accepted as a more appropriate representation of uncertainty from the RIO perspective.

Figure 2: The final chosen RIO distribution for QoI 1



Abbreviations: RIO, Rational Impartial Observer; QoI, quantity of interest.

Table 2: Percentiles from the fitted RIO distribution for QoI 1

Percentile	1%	2.5%	10%	25%	50%	75%	90%	97.5%	99%
Value (out of 1000)	27	45	77	104	130	153	171	190	200

Abbreviations: RIO, Rational Impartial Observer; QoI, quantity of interest.

6. QUANTITY OF INTEREST 2

The second quantity of interest (QoI 2) was defined as: for the PCP subgroup population from the IMCgp100-202 trial in **the pembrolizumab arm (excluding effect of tebentafusp as a subsequent treatment)**, the proportion of patients, expressed as a number per 1000, who are still alive at year 8 after randomisation.

6.1 Individual judgements

The Facilitator asked the experts to provide their judgments for the lower plausible limit, upper plausible limit, median, lower quartile (Q1), and upper quartile (Q3). Table 3 shows the experts' individual judgements for QoI 2.

Table 3: Experts' individual judgements for QoI 2

Expert	**Lower plausible limit**	**Lower quartile**	**Median**	**Upper quartile**	**Upper plausible limit**
G	50	90	100	110	150
H	20	45	60	75	140
I	10	80	120	140	180
J	50	75	100	135	200

Expert	Lower plausible limit	Lower quartile	Median	Upper quartile	Upper plausible limit
K	20	40	65	100	160

Abbreviations: QoI, quantity of interest.

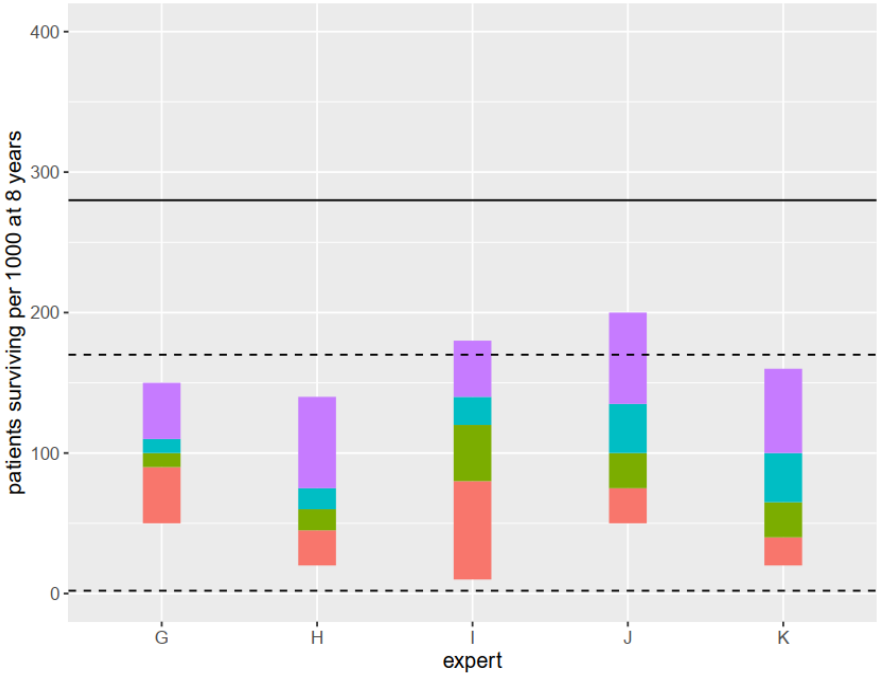
6.2 Scenario testing

After the experts' individual judgements had been recorded, the experts were presented with an extrapolation based on a particular scenario, this was a repeat of the exercise discussed in Section 5.2. It was explained to the experts that the aim of presenting the scenario was to give a point of reference for reflection on their individual judgements: no claims were made by the elicitation team regarding the probability of the scenario being true.

The scenario was that the hazard remained unchanged from year 3 onwards. Based on this, an approximate 95% credible interval was reported for the survival at 8 years to indicate what range of values would be statistically consistent with the assumption of no change in the hazard. Experts were invited to reflect on whether their plausible ranges exceeded either interval limit, and this provided a starting point for the group discussion. The experts' judgements and the 95% credible interval corresponding to the constant hazard scenario are shown in Figure 3.

Figure 3: Individual quartile judgements for QoI 2

(For each expert, each coloured section represents a range judged to contain the true QoI with probability 25%. Values outside the range indicated by the four coloured sections were not judged to be plausible. The solid line is the upper Kaplan-Meier 97.5% confidence limit for survival at 4 years. The dashed lines show an approximate 95% interval for survival at 8 years that is statistically consistent with a scenario of no change in hazard from year 3 onwards.)



Abbreviations: QoI, quantity of interest.

6.3 Group discussion

At the onset of the group discussion, some experts expressed that they now understood the group members' methodology and felt this could alter their initial individual judgements. The Facilitator stressed that individual judgements should be made according to the experts' individual opinion not in anticipation of the group discussion and/or RIO judgement.

The Facilitator invited the experts to discuss their view on the relative effect between tebentafusp and pembrolizumab. All experts believed that tebentafusp has a greater effect compared to pembrolizumab and is a more favourable treatment due to minimal side effects associated with tebentafusp and the stability of patients even post-progression.

It was noted by experts that patient response to immunotherapies is not as predictable in UM as opposed to cutaneous melanoma (CM) and that this is due to CM and UM being biologically distinct cancers. The experts also commented that there are currently no known predictors for which UM patients would be likely to respond to pembrolizumab. The experts further clarified this by citing the mutational burden of UM being relatively low compared to CM. Pembrolizumab is more effective in tumours with high mutational burden such as CM. As there are fewer tumour mutations in UM, it was not surprising to the experts that pembrolizumab is less effective for many UM patients. The experts expressed their opinion that the novel method of action of tebentafusp, as opposed to immunotherapies such as pembrolizumab, would potentially make response more durable in UM patients, even after radiological progression.

The Facilitator invited the experts to discuss the potential factors that could contribute to decreasing and increasing hazards. The experts discussed the notion that most patients who are going to die will do so within the first 2 years and the remaining patients form a sub-population of longer-term survivors. This longer-term survival was attributed to disease and patient biology and thus applies to both arms and supports the notion of decreasing hazards. The experts expressed that a proportion of patients who respond to pembrolizumab may experience good disease control.

The experts highlighted that despite the presence of longer-term survivors in the pembrolizumab arm, it would be expected that these form a lower proportion compared to those observed in the tebentafusp arm.

Regarding the potential for increasing hazards, the experts discussed the potential for long-term toxicity effects which would result in an increased risk for patients but stated this to be relatively rare for single-agent immunotherapies. Age and patient comorbidities were also noted as potential contributors towards an increasing hazard.

The Facilitator checked with the experts if there are additional comments regarding cross-over. The experts confirmed no further comments.

6.4 Reflection after discussion

The experts were each asked to reflect on the discussion that had taken place thus far, and comment on whether they had changed their position from their initial judgements.

G: no change to initial judgements This expert also noted that the more aligned judgements could be attributed to the learning of the methodology within the workshop as well as a greater knowledge base for this intervention.

H: no change to initial judgements.

I: expressed that they would increase their lower plausible limit by a small amount.

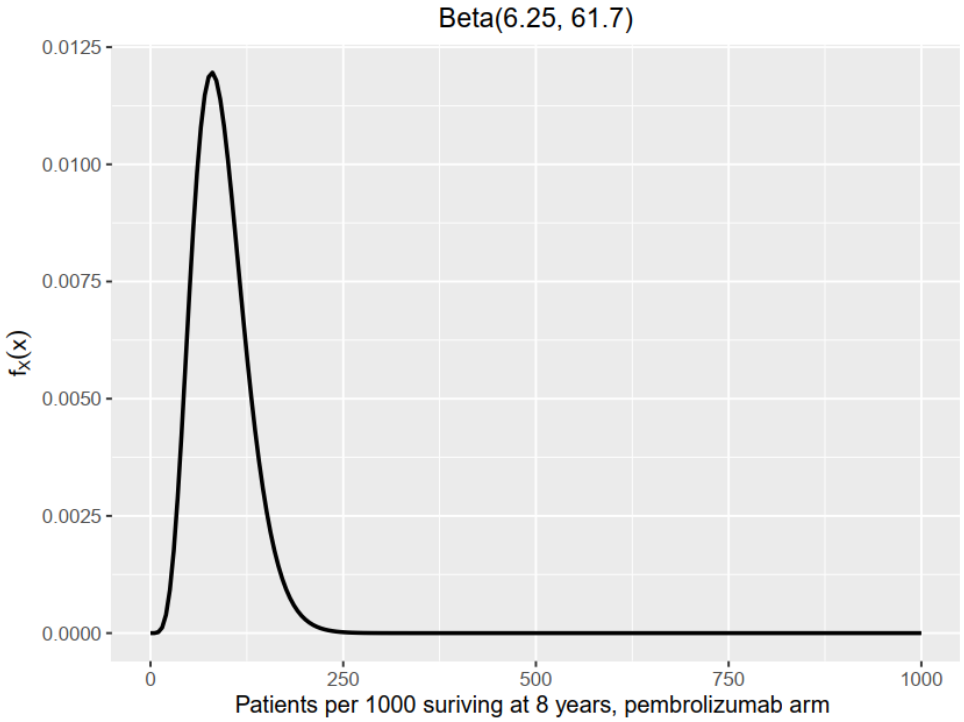
J: reflected that their judgements are “optimistic but uncertain” and proposed no change to their initial judgements.

K: no change to initial judgements.

6.5 RIO judgements and distribution

The experts were asked to consider probability judgements that would be made by a RIO, as for the previous QoI. In this case, as there was little disagreement between the experts, the Facilitator proposed assuming the initial RIO judgements to be the median and quartiles computed as averages of the experts’ initial judgements. A beta distribution was fitted to these judgements and shown to the experts (see Figure 4). The percentiles from the fitted RIO distribution for QoI 2 are presented in Table 4.

Figure 4: The final RIO distribution for QoI 2



Abbreviations: RIO, Rational Impartial Observer; QoI, quantity of interest.

Table 4: Percentiles from the fitted RIO distribution for QoI 2

Percentile	1%	2.5%	10%	25%	50%	75%	90%	97.5%	99%
Value (out of 1000)	29	36	51	67	88	113	139	171	189

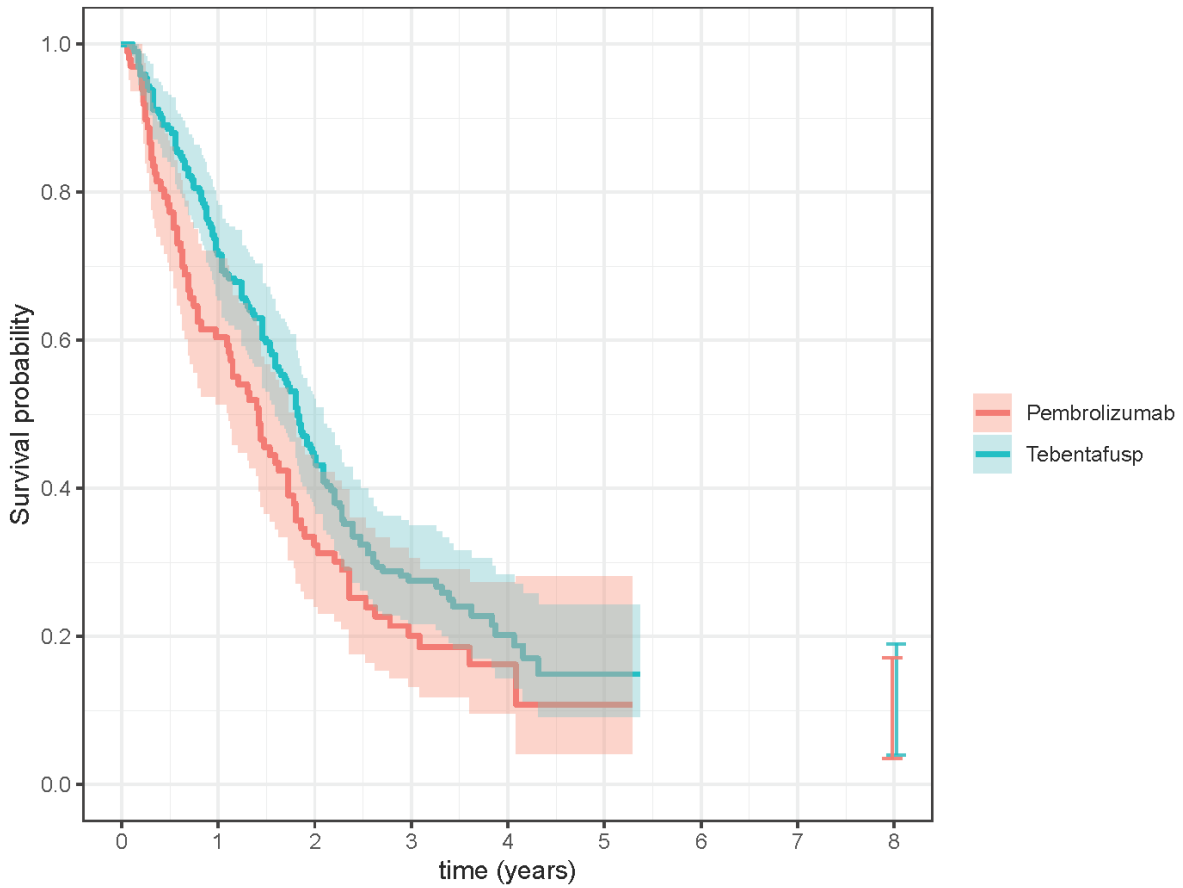
Abbreviations: RIO, Rational Impartial Observer; QoI, quantity of interest.

The RIO distribution and percentiles were shown to the experts, and it was agreed by all experts that the RIO distribution was an appropriate representation of uncertainty.

7. SUMMARY OF ELICITED QOI 1 AND QOI 2

Figure 5 presents the Kaplan-Meier curve for the PCP subgroup population from the IMCgp100-202 trial (DCO June 2023) for both treatment arms using reconstructed individual patient-level data and the elicited 95% credible intervals at 8 years post-randomisation.

Figure 5: Kaplan-Meier plots and elicited 95% credible intervals for the survival at 8 years (offset slightly from 8 years for visibility) for the PCP subgroup



Abbreviations: PCP, pre-choice pembrolizumab.

8. COMMENT ON THE CHOSEN TIME POINT FOR QOIS

The Chair invited the experts to provide their view on the chosen time point for the elicitation exercises (8 years) as this deviated from the commonly used landmark timepoints in survival analysis (e.g. 5 and 10 years). The experts reported no challenge in using a time point that differs from the standard landmark review and stated that the landmark timepoints are often used out of tradition and that trials are more commonly reporting data periodically which therefore does not conform to the traditional landmark time points.

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APPENDIX 1: EXPERTS' EXPERTISE AREA AND DECLARATION OF CONFLICTS OF INTEREST

Expert name	Expertise Area	Conflicts of interest
Dr Clare Barlow	Medical Oncology consultant. Immunotherapy Service Lead for SFT. Provides liver surveillance for high risk ocular melanoma patients and treatment for metastatic disease for almost 15 years (since July 2009). (Somerset Foundation Trust)	Sponsorship for educational meetings/Advisory Board honoraria/speaker fees Merck Sharpe Dohme and Bristol Myers Squibb.
Dr Steve Nicholson	Consultant oncologist with responsibility for management of melanoma (cutaneous & non-cutaneous) and rare urological malignancy (testis, penis, renal). 22 years experience managing melanoma at consultant level. (Mid & South Essex NHS Foundation Trust)	None
Dr Miranda Payne	Consultant Medical Oncologist specialising in melanoma for the last 10 years. (Oxford University Hospitals NHS Foundation Trust)	Speaker fees and funding to attend conferences from Bristol-Myers Squibb and Merck Sharp & Dohme.
Dr Rachel Plant	Consultant Medical Oncologist with interest in melanoma for 5 years. (University Hospital Dorset)	None
Dr Dulani Ranatunge	Consultant Medical Oncologist. Manages skin cancers, specialising in melanoma including uveal melanoma for 6 years. (Queens Center for Oncology, Hull University teaching Hospital)	None

APPENDIX 2: COMPANY RESPONSE TO EAP/COMMERCIAL PRODUCT QUERIES

Background: The clinical study IMCgp100-202 was closed in October 2022. Follow up data were collected for survival and subsequent treatments using a separate electronic Clinical Outcomes Assessment (eCOA) platform (YPrime Inc). With the exception of Germany, all countries permitted continued follow up after closure of the clinical trial. Unfortunately, the Germany Health Authority / Regulator did not allow follow up of patients outside the clinical trial and the remaining German patients were lost to follow due to *'sponsor ended study*'. At the time the trial was closed, in Germany 15 patients were alive and lost to follow up (12 in tebentafusp arm and 3 control arm who received pembrolizumab as investigator's choice).

1. Definition of time to treatment discontinuation (Figure 10 in the document [ID1441_company_ACD_response_Addendum 2_updated B3_v0.2 190423 ACIC]). Some people who received tebentafusp as part of the IMCgp100-202 trial as a 1st line therapy continued to receive it as part of the EAP.

Company response: In the above document, the text that refers to Figure 10 states "*In the tebentafusp PCP subgroup, 172 (86%) events out of 192 patients were observed*". The data were considered mature at the time of data cut-off on April-2022. Note, the title of the document above is different to the one we have in our records.

At the time the study closed (October 2022), 232 (97%) of 245 patients who had received tebentafusp had discontinued treatment and 181 (94%) of 192 patients from the *tebentafusp PCP subgroup* had discontinued treatment. At the time the study closed (October 2022), patients receiving tebentafusp were switched to either the EAP or commercial product, dependent on the country. Patients were not followed up for a date of discontinuation with tebentafusp because the data were considered very mature at the time the study was closed.

2. How were these people dealt with when calculating time to treatment discontinuation? Were they censored at the time they moved to EAP?

Company response: patients were censored for analysis of treatment discontinuation when the study was closed i.e. censored when they were switched to either commercial product or the EAP.

3. How was the OS dealt with in this type of patient? Were they censored at the time they moved to the EAP?

Company response: With the exception of patients in Germany, patients were followed up for survival (OS) using the eCOA platform from October 2022 (see above). Follow up for OS was independent of the EAP. After 3 years of follow up of the last patient recruited to the trial, data for the 3-year analysis was published (Hassel *et al.* 2023). Patients continue to be followed up for OS today. OS data for patients in Germany lost to follow up due to '*sponsor ended study*' were censored for analysis of OS at the time the study closed. The time points for censoring of OS for the 12 patients from the tebentafusp arm were between 27.5 and 49 months.

At the time of the 3-year analysis, 37 patients remained alive and in follow up in the tebentafusp arm of which 29 patients were in the *tebentafusp PCP subgroup*. In the control group, 11 patients remained alive, all received prior pembrolizumab as investigator's choice and 5 of the 11 received tebentafusp as a subsequent treatment.

APPENDIX 3: COMPANY RESPONSE TO SUBSEQUENT TREATMENTS QUERIES

The table including subsequent treatments used for patients in the pembrolizumab arm is shown below. Note, some patients received multiple (2) subsequent therapies. A total of 25 patients from the pembrolizumab sub-group of the Investigator's Choice arm received tebentafusp (IMCGP100) as a subsequent treatment following pembrolizumab.

In addition, a large proportion of patients received a subsequent immunotherapy (CTLA4, PD1, PD1/other) other than tebentafusp. During the second committee meeting, one of the committee members noted that the guidance for melanoma did not recommend for a second immunotherapy if a patient has received a prior immunotherapy.

Table 5 Summary of subsequent therapies (ITT population, DCO April 2023)

Subsequent	Tebentafusp	Dacarbazine	Ipilimumab	Pembrolizumab	Investigator's	Overall
Systemic	151 (59.9)	3 (42.9)	9 (56.3)	64 (62.1)	76 (60.3)	227 (60.1)
Chemotherapy	45 (17.9)	2 (28.6)	2 (12.5)	14 (13.6)	18 (14.3)	63 (16.7)
Immunotherapy	133 (52.8)	3 (42.9)	6 (37.5)	52 (50.5)	61 (48.4)	194 (51.3)
CTLA4	87 (34.5)	0	3 (18.8)	27 (26.2)	30 (23.8)	117 (31.0)
PD1	119 (47.2)	3 (42.9)	3 (18.8)	32 (31.1)	38 (30.2)	157 (41.5)
PD1/Other	1 (0.4)	0	0	2 (1.9)	2 (1.6)	3 (0.8)
Other immunotherapies	19 (7.5)	0	2 (12.5)	26 (25.2)	28 (22.2)	47 (12.4)
IMCgp100	0	0	2 (12.5)	25 (24.3)	27 (21.4)	27 (7.1)
Other	19 (7.5)	0	0	4 (3.9)	4 (3.2)	23 (6.1)
Other systemic therapies	4 (1.6)	0	0	2 (1.9)	2 (1.6)	6 (1.6)
Targeted	20 (7.9)	2 (28.6)	1 (6.3)	11 (10.7)	14 (11.1)	34 (9.0)
Local therapy	27 (10.7)	0	7 (43.8)	15 (14.6)	22 (17.5)	49 (13.0)
Radiotherapy	35 (13.9)	1 (14.3)	4 (25.0)	19 (18.4)	24 (19.0)	59 (15.6)
Surgery	1 (0.4)	0	0	1 (1.0)	1 (0.8)	2 (0.5)
Other therapies*	4 (1.6)	0	0	2 (1.9)	2 (1.6)	6 (1.6)

* Other therapies include: ALL OTHER THERAPEUTIC PRODUCTS, ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS, CAR T-CELLS NOS, CDX 1140, IMCGP 100, INVESTIGATIONAL ANTINEOPLASTIC DRUGS, M 6223, NELITOLIMOD, Not Coded, RELATLIMAB, TALIMOGENE LAHERPAREPVEC, TIRAGOLUMAB

Online Workshop Report

Expert elicitation in response to an upheld appeal (NICE technology appraisal ID1441, tebentafusp for advanced uveal melanoma)

REPORT BY THE DECISION SUPPORT UNIT

May 2024

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ABBREVIATIONS

ACM	Appraisal committee meeting
CM	Cutaneous melanoma
DCO	Data cut-off
EAP	Expanded access programme
ITT	Intention to treat
HLA	Human leukocyte antigen
PCP	Pre-choice pembrolizumab
PFS	Progression-free survival
OS	Overall survival
RIO	Rational Impartial Observer
UM	Uveal melanoma
QoI	Quantity of Interest
TA	Technology appraisal
TTD	Time to treatment discontinuation

1. BACKGROUND

Two NICE appraisal committee meetings (ACMs) were held to discuss NICE single technology appraisal (TA) ID1441, tebentafusp for advanced uveal melanoma (UM).[1] The draft final appraisal decision was that tebentafusp was not deemed to be cost-effective and would not be recommended for the Cancer Drugs Fund.[1]

An appeal hearing was held on 20 October 2023, which was upheld on several points. All of the upheld points related to the appeal panel's expectation that, faced with significant uncertainty, the input of experts should be particularly important in informing the committee's judgements.

The aim of the elicitation workshop is to address one of the upheld appeal points relating to the long-term overall survival (OS).

2. WORKSHOP INFORMATION

Date	17 April 2024
Format	Online (10:00-15:15 including 1.5 hours training)
Expert participants*	Dr Jenny Nobes (Norfolk and Norwich University Hospital) Dr Bode Oladipo (Belfast Health and Social Care trust) Dr Lalit Pallan (University Hospitals Birmingham NHS FT) Dr Kate Scatchard (Royal Devon University Hospitals NHS Trust) Dr Patricio Serra (The Christie NHS Foundation Trust) Dr Heather Shaw (University College London Hospitals and Mount Vernon Cancer Centre)
Chair	Dr Kate (Shijie) Ren (University of Sheffield)
Facilitator	Professor Jeremy Oakley (University of Sheffield)
Recorder	Dr Jessica Forsyth (University of Sheffield)
Quantity of Interest (QoI)	**QoI 1** For the pre-choice pembrolizumab (PCP) subgroup population from the IMCgp100-202 trial in **the tebentafusp arm**, the proportion of patients, expressed as a number per 1000, who are still alive at year 8 after randomisation. **QoI 2** For the pre-choice pembrolizumab (PCP) subgroup population from the IMCgp100-202 trial in **the pembrolizumab arm (excluding effect of tebentafusp as a subsequent treatment)**, the proportion of patients, expressed as a number per 1000, who are still alive at year 8 after randomisation.
Elicitation protocol	The Sheffield Elicitation Framework (SHELF)[2]

* Note: expertise and declaration of conflicts of interest are presented in Appendix 1: Experts' expertise area and declaration of conflicts of interest.

3. MOTIVATION AND TRAINING

Experts were given a presentation on the background of the project and the motivation for using probability distributions to represent uncertainty. Experts received training on general probability elicitation, biases in probability judgements, and survival extrapolation including survivor and hazard functions and their qualitative interpretation. A practice exercise on eliciting long-term survival data for lung cancer patients who quit smoking was carried out.

4. EVIDENCE

An Evidence Dossier was compiled,[3] which included the following data from the IMCgp100-202 trial for both the tebentafusp and pembrolizumab arm

- Baseline characteristics
- OS for the PCP subgroup (June 2023)
- Time to treatment discontinuation (TTD) for the PCP subgroup (April 2022)
- Progression-free survival (PFS) for the intention to treat (ITT) group (August 2021)

The Evidence Dossier also included the following supporting documents

- IMCgp100-202 trial evidence
  - Hassel *et al.* 2023[4]
  - Nathan *et al.* 2021[5]
- IMCgp100-102 trial evidence
  - Carvajal *et al.* 2022[6]
- External evidence
  - Meta-analyses: Rantala *et al.* 2019[7], Khoja *et al.* 2019[8]
  - Data for tebentafusp: Petzold *et al.* 2023[9], Piulats *et al.* 2023[10], Orloff *et al. 2023*[11]
  - Data for other interventions: Wolchok *et al.* 2022[12], Piulats *et al.* 2021[13], Rantala *et al.* 2020[14], Bol *et al.* 2019[15], Heppt *et al.* 2019[16], Rossi *et al.* 2019[17], Schadendorf *et al.* 2015[18]

5. QUANTITY OF INTEREST 1

The first quantity of interest (QoI 1) was defined as: for the PCP subgroup population from the IMCgp100-202 trial in **the tebentafusp arm**, the proportion of patients, expressed as a number per 1000, who would still be alive at year 8 after randomisation.

5.1 Individual judgements

The Facilitator asked the experts to provide their judgments for the lower plausible limit, upper plausible limit, median, lower quartile (Q1), and upper quartile (Q3). The experts were asked to make their judgements independently, without conferring.

Table 1 shows the experts' individual judgements for QoI 1.

Table 1: Experts' individual judgements for QoI 1

Expert	Lower plausible limit	Lower quartile	Median	Upper quartile	Upper plausible limit
A	90	110	150	190	240
B	15	60	80	110	180
C	80	150	180	200	250
D	5	75	100	150	175
E	25	50	150	175	200
F	60	100	130	145	170

Abbreviations: QoI, quantity of interest.

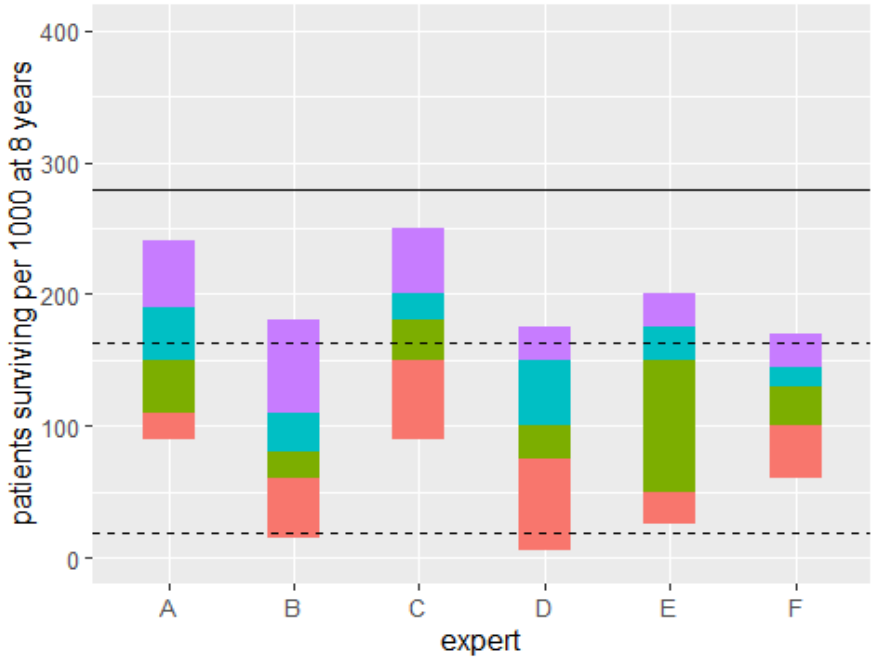
5.2 Scenario testing

After the experts' individual judgements had been recorded, the experts were presented with an extrapolation based on a particular scenario. It was explained to the experts that the aim of presenting the scenario was to give a point of reference for reflection on their individual judgements: no claims were made by the elicitation team regarding the probability of the scenario being true.

The scenario was that the hazard remained unchanged from year 3 onwards. An exponential model was fitted to the 3-4 years survival data and extrapolated to 8 years. Based on this, an approximate 95% credible interval was reported for the survival at 8 years, to indicate what range of values would be statistically consistent with the assumption of no change in the hazard. The experts were invited to reflect on whether their plausible ranges exceeded either interval limit, and this provided a starting point for the group discussion. The experts' judgements and the 95% credible interval corresponding to the constant hazard scenario are shown in

Figure 1.

Figure 1: Individual quartile judgements for QoI 1
(For each expert, each coloured section represents a range judged to contain the true QoI with probability 25%. Values outside the range indicated by the four coloured sections were not judged to be plausible. The solid line is the upper Kaplan-Meier 97.5% confidence limit for survival at 4 years. The dashed lines show an approximate 95% credible interval for survival at 8 years that is statistically consistent with a scenario of no change in hazard from year 3 onwards.)



Abbreviations: QoI, quantity of interest.

5.3 Group discussion

A facilitated group discussion between the experts followed.

The experts sought clarification of the TTD definition with respect to patients continuing tebentafusp treatment via the expanded access programme (EAP). The experts queried whether patients who initially received tebentafusp as part of the IMCgp100-202 trial but then transferred to receive tebentafusp via an EAP would be identified as “discontinuing treatment”. Experts highlighted that this was not clear in the Evidence Dossier and stressed that the team should seek clarification from the company for the face-to-face workshop.

The Chair confirmed that this was not defined clearly in the Evidence Dossier and would clarify with the company before the face-to-face workshop, the company’s response (received after the workshop) is included in

Appendix 2: Company response to EAP/commercial product queries for reference. The experts queried whether the QoI definition allowed for patients to continue treatment with tebentafusp after year four, the Chair confirmed that the QoI definition allows this. All experts confirmed that they considered patients continuing tebentafusp treatment after year four post-randomisation when making individual judgements.

The Facilitator invited the experts to discuss the potential factors contribute to increasing and decreasing hazards.

The experts agreed that decreasing hazards was plausible, on the basis that there is a potential subgroup of longer-term survivors whose biology generally results in longer survival times irrespective of treatment received. Although not discussed until the elicitation of QoI 2, the experts commented on the observed higher response rate for treating with tebentafusp compared to pembrolizumab. A first in class treatment with an improved response rate would therefore have potential for a reduced hazard in the long-term and support the notion of a decreasing hazard.

The Facilitator invited the experts to discuss cure plausibility. The experts thought both tebentafusp and pembrolizumab are not curative treatments and that longer-term data would be required before a cure would be considered.

Potential factors put forward by experts for increasing hazard included medical comorbidities, aging and subsequent therapy administration becoming less effective over time.

5.4 Reflection after discussion

The experts were each asked to reflect on the discussion that had taken place thus far, and comment on whether they had changed their position from their initial judgements.

A: believed that their initial judgements on the lower plausible limit may be too optimistic and would reduce their estimates due to the consideration of the trial population, the presence of long-term survivors, and that they no longer believe it was implausible to see 5% survival at 8 years.

B: was satisfied with their initial judgements and stated that their estimates are higher than those that would be expected in an untreated population.

C: thought they had been too optimistic initially, and would adjust their judgements towards those of expert B.

D: believed their estimates were slightly pessimistic and would increase their judgement of the upper quartile. Otherwise, they remained confident the QoI would be within their plausible range.

E: was satisfied with their plausible range, but would modify their judgements of the lower and upper quartiles due to their relative position to the median (i.e., they would move the quartiles closer to the median).

F: expressed that they would decrease their lower plausible limit.

5.5 RIO judgements and distribution

The experts were then asked to consider a single set of probability judgements that would appropriately represent the views and evidence presented. Specifically, they were asked to propose a set of probabilities from the perspective of a “Rational Impartial Observer” (RIO):

an individual who has listened to all the discussion and seen all the evidence and would impartially consider their own uncertainty based on this. It was explained that "RIO's distribution" would be presented as the conclusion from the workshop, but that any dissenting views of individual experts would be noted.

The Facilitator asked the experts what probability RIO would give to the survival being less than 100 patients per 1000 at 8 years post-randomisation. A 50% probability was first proposed by experts and was considered in the first instance.

The Facilitator asked the experts what probability RIO would give to the survival being less than 50 out of 1000 at 8 years post-randomisation. The experts thought this would be unlikely due to the presence of longer-term survivors, the natural biology of the disease, and the trial population being generally healthier compared to the general population. Probabilities in the range 10%-20% were proposed.

The Facilitator asked the experts what chance RIO would give to the survival being greater than 150 per 1000 at 8 years post-randomisation. Probabilities in the range 10% to 30% were suggested.

The Facilitator first fitted a Beta distribution to the following RIO judgements using the SHELF R package[19]

- 10% probability that survival is below 50 per 1000
- 50% probability that survival is greater than 100 per 1000
- 10% probability that survival is greater than 150 per 1000

This resulted in a Beta(5.69, 49.80) distribution for the QoI, which was presented to the experts. The 1st and 99th percentiles of this distribution were 31 per 1000 and 216 per 1000 respectively. The experts thought these percentiles were too extreme at each end. The experts believed that given the trial evidence, the upper limit implied by this distribution was too optimistic and that they would expect a greater reduction in the number of patients alive after a further 4 years.

Revised RIO judgements were considered.

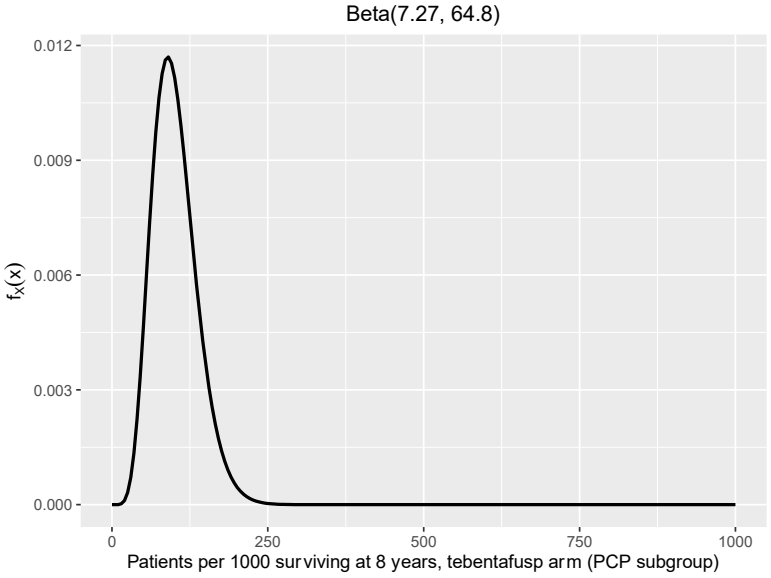
- 10% probability that survival is below 50 per 1000
- 50% probability that survival is greater than 100 per 1000
- 5% probability that survival is greater than 150 per 1000

and a Beta distribution was fitted and shown to the experts (See

). The percentiles from the fitted RIO distribution are presented in Table 2.

One expert felt that there was a case for more uncertainty than that implied by this distribution and stressed that they know little regarding the long-term effects of tebentafusp. The other experts thought this was a reasonable representation of the group's uncertainty and was reflective of the trial cohort fitness.

Figure 2: The final chosen RIO distribution for QoI 1



Abbreviations: RIO, Rational Impartial Observer; QoI, quantity of interest.

Table 2: Percentiles from the fitted RIO distribution for QoI 1

Percentile	**1%**	**2.5%**	**10%**	**25%**	**50%**	**75%**	**90%**	**97.5%**	**99%**
Value (out of 1000)	36	43	59	75	97	123	148	180	198

Abbreviations: RIO, Rational Impartial Observer; QoI, quantity of interest.

6. QUANTITY OF INTEREST 2

The second quantity of interest (QoI 2) was defined as: for the PCP subgroup population from the IMCgp100-202 trial in **the pembrolizumab arm (excluding effect of tebentafusp as a subsequent treatment)**, the proportion of patients, expressed as a number per 1000, who are still alive at year 8 after randomisation.

6.1 Individual judgements

The Facilitator asked the experts to provide their judgments for the lower plausible limit, upper plausible limit, median, lower quartile (Q1), and upper quartile (Q3).
Table 3 shows the experts' individual judgements for QoI 2.

Table 3: Experts' individual judgements for QoI 2

Expert	**Lower plausible limit**	**Lower quartile**	**Median**	**Upper quartile**	**Upper plausible limit**
A	20	40	100	120	150
B	15	50	60	90	150
C	20	60	80	110	150
D	35	50	60	90	150
E	20	50	80	120	160
F	20	36	60	80	100

Abbreviations: QoI, quantity of interest.

6.2 Scenario testing

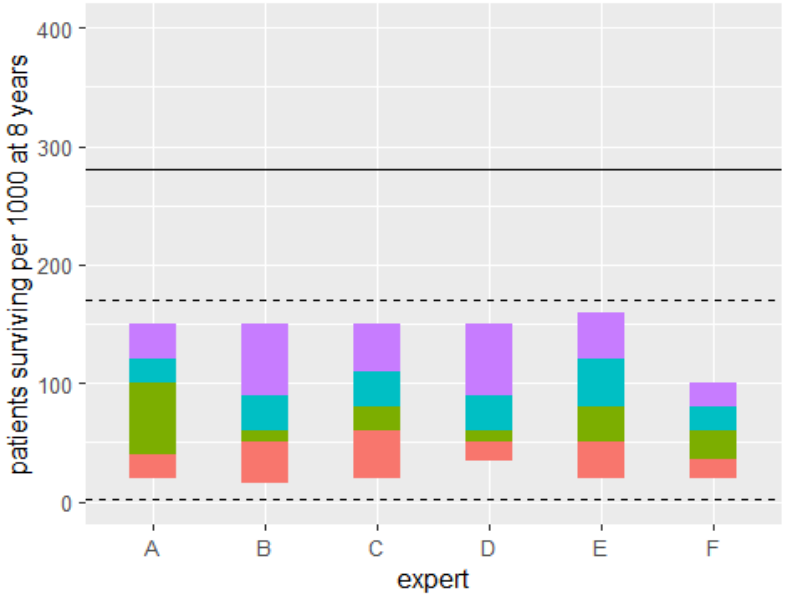
After the experts' individual judgements had been recorded, the experts were then presented with an extrapolation based on a particular scenario, this was a repeat of the exercise discussed in Section 5.2. It was explained to the experts that the aim of presenting the scenario was to give a point of reference for reflection on their individual judgements: no claims were made by the elicitation team regarding the probability of the scenario being true.

The scenario was that the hazard remained unchanged from year 3 onwards. Based on this, an approximate 95% credible interval was reported for the survival at 8 years to indicate what range of values would be statistically consistent with the assumption of no change in the hazard. Experts were invited to reflect on whether their plausible ranges exceeded either interval limit, and this provided a starting point for the group discussion. The experts' judgements and the 95% credible interval corresponding to the constant hazard scenario are shown in

Figure **3**.

Figure 3: Individual quartile judgements for QoI 2

(For each expert, each coloured section represents a range judged to contain the true QoI with probability 25%. Values outside the range indicated by the four coloured sections were not judged to be plausible. The solid line is the upper Kaplan-Meier 97.5% confidence limit for survival at 4 years. The dashed lines show an approximate 95% credible interval for survival at 8 years that is statistically consistent with a scenario of no change in hazard from year 3 onwards.)



Abbreviations: QoI, quantity of interest.

6.3 Group discussion

The Facilitator invited the experts to discuss their view on the relative effect between tebentafusp and pembrolizumab. From the data available, all the experts were confident that tebentafusp is more effective than pembrolizumab for UM patients, referencing the number of responders across the two arms. The experts believed that the relative efficacy of tebentafusp would exist outside of the trial population, in the real-world setting. All experts believed that there would still be a difference in OS between the tebentafusp-PCP and pembrolizumab arms at 8 years post randomisation.

The experts highlighted that plateaus in OS are not typically present for advanced UM patients even with treatment with checkpoint inhibitors, whereas there is often a plateau in survival curves for cutaneous melanoma (CM) patients. The experts reiterated that this should be considered when comparing the relative effect as UM and CM are different cancers.

The Facilitator invited the experts to discuss the potential factors contribute to increasing and decreasing hazards.

The experts first discussed, with respect to a decreasing hazard, the subsequent treatment of pembrolizumab patients with tebentafusp but acknowledged that this effect should not be considered for QoI 2. Experts further discussed that in the pembrolizumab arm there would be the same presence of long-term survivors (as discussed for the tebentafusp arm). This was accredited to the fact that the patients in the pembrolizumab arm are from the same base population and that the presence of these patients would therefore contribute to decreasing hazards for both arms. It was noted that UM patients treated with pembrolizumab typically have very low response rates, therefore survival at these extrapolated time points is likely to be driven predominantly by the biology of the disease and not the treatment with pembrolizumab, which could in theory result in a decreasing hazard.

Cure plausibility was commented on for the previous QoI: tebentafusp and pembrolizumab were not considered to be curative treatments by experts.

Regarding the potential for increasing hazard, it was noted by experts that if the volume of the disease increases, the general fitness of patients will likely decrease, therefore the burden on the patient will increase and thus the hazard will ultimately increase.

The Facilitator asked if the experts might expect zero survivors at a time point earlier than 8 years, but this was not thought to be plausible.

The Facilitator checked with the experts if there are additional comments regarding cross-over. The experts confirmed no further comments.

6.4 Reflection after discussion

The experts were each asked to reflect on the discussion that had taken place thus far, and comment on whether they had changed their position from their initial judgements.

A: no revision to initial judgements and stated that patients' disease is not static. This expert also mentioned the competing risks of the disease and treatment and therefore does not believe that the hazard will decrease and thus is confident with estimate.

B: no revision, confident in personal estimates.

C: no revision, confident in personal estimates.

D: no revision, confident in personal estimates.

E: no revision, confident in personal estimates.

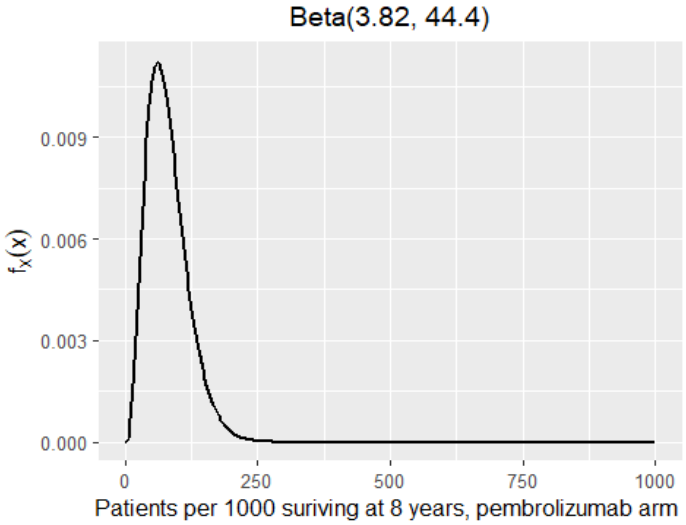
F: expressed that they would increase the upper plausible limit slightly to 120 to be more in line with other experts' values.

6.5 RIO judgements and distribution

The experts were asked to consider probability judgements that would be made by a RIO as for the previous QoI. In this case, as there was little disagreement between the experts, the Facilitator proposed assuming initial RIO judgements to be the median and quartiles computed as averages of the experts' individual judgements. A beta distribution was fitted to these judgements and shown to the experts (see Figure 4). The percentiles from the fitted RIO distribution for QoI 2 are presented in Table 4.

There were no concerns of overconfidence; the experts thought this distribution was an appropriate reflection of the disease biology and what is observed within clinic. The experts noted that more data are available for treatment with pembrolizumab. The experts reiterated that there is no evidence of a plateau effect in advanced UM patients when treated with pembrolizumab, whereas this is less certain for tebentafusp and that the RIO distribution for QoI 2 captures this.

Figure 4: The final RIO distribution for QoI 2



Abbreviations: RIO, Rational Impartial Observer; QoI, quantity of interest.

Table 4: Percentiles from the fitted RIO distribution for QoI 2

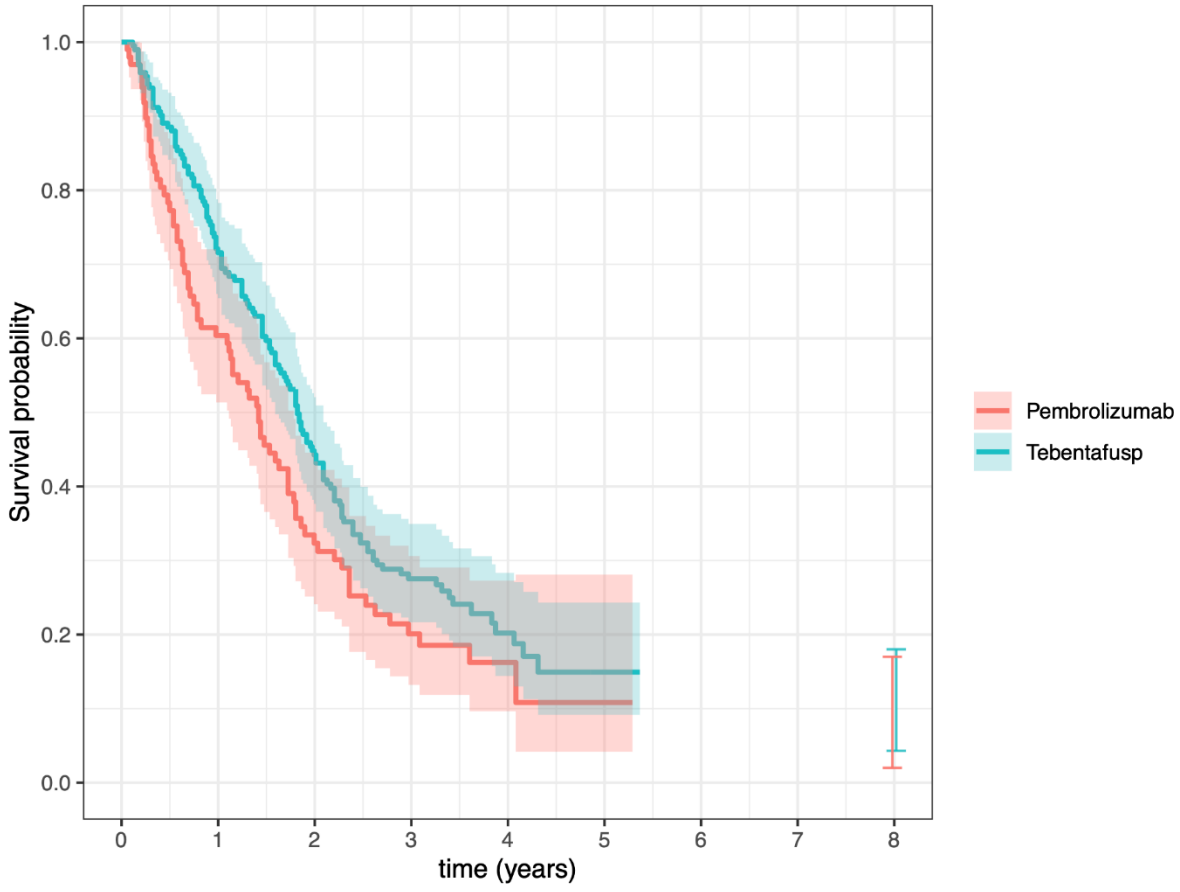
Percentile	**1%**	**2.5%**	**10%**	**25%**	**50%**	**75%**	**90%**	**97.5%**	**99%**
Value (out of 1000)	16	22	35	51	74	102	131	169	192

Abbreviations: RIO, Rational Impartial Observer; QoI, quantity of interest.

7. SUMMARY OF ELICITED QOI1 AND QOI2

Figure 5 presents the Kaplan-Meier curve for the PCP subgroup population from the IMCgp100-202 trial (DCO June 2023) for both treatment arms using reconstructed individual patient-level data and the elicited 95% credible intervals at 8 years post-randomisation.

Figure 5: Kaplan-Meier plots and elicited 95% credible intervals for the survival at 8 years (offset slightly from 8 years for visibility) for the PCP subgroup



Abbreviations: PCP, pre-choice pembrolizumab.

8. COMMENT ON THE CHOSEN TIME POINT FOR QOIS

The Chair invited the experts to provide their view on the chosen time point for the elicitation exercises (8 years) as this deviated from the commonly used landmark timepoints in survival analysis (e.g. 5 and 10 years). The experts felt that there was no additional challenge in using this time point.

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APPENDIX 1: EXPERTS' EXPERTISE AREA AND DECLARATION OF CONFLICTS OF INTEREST

Expert name	Expertise Area	Conflicts of interest
Dr Jenny Nobes	Consultant Oncologist since 2010. (Norfolk and Norwich University Hospital)	Received honorarium May 2023 from Immunocore for talk at Melanoma Focus meeting.
Dr Bode Oladipo	Consultant Medical Oncologist treating melanoma including uveal. 12.5 years experience. (Belfast Health and Social Care trust)	Received honorarium for participation in advisory board and educational meetings from both Merck Sharp & Dohme and Bristol-Myers Squibb. Involved in the national tebentafusp expanded access programme.
Dr Lalit Pallan	Consultant Medical Oncologist, specialising in Melanoma. In post since 2020. See patients with high risk of primary uveal melanoma to co-ordinate follow up and screening investigations for metastatic disease. (University Hospitals Birmingham NHS FT)	Received speaker fees from Bristol-Myers Squibb. PI on Immunocore clinical trial in cutaneous melanoma – ongoing (MEL-203).
Dr Kate Scatchard	13 years of experience. Undertake surveillance for a larger cohort of uveal melanoma patients. (Royal Devon University Hospitals NHS Trust)	None
Dr Patricio Serra	Consultant Medical Oncologist, experience in the field of melanoma for over 8 years. Experience with patients with melanoma, cutaneous, mucosal and uveal in the early stages and advanced stages of cancer. Specialist Skin Multi-disciplinary team (SSMDT) chair where the management of melanoma cases are discussed. (The Christie NHS Foundation Trust)	Fees received as Speaker for Bristol-Myers Squibb.
Dr Heather Shaw	Consultant medical oncologist treating melanoma and skin cancers with a specific interest in UM. Consultant for 7 years. Currently the National Coordinating Investigator for two clinical trials with a specific focus on UM. A contributing oncologist to national UM guidelines. Treated many patients with tebentafusp (and with its cousin	Provided speaker services, advisory board input and has run/ is running clinical trials for Bristol-Myers Squibb, Immunocore, Merck Sharp & Dohme. No involvement in any advisory meetings on the current appraisal to date (ID1441).

	molecule in development) and have significant experience of the clinical pathway these patients follow. (University College London Hospitals and Mount Vernon Cancer Centre)	Registered practitioner on previously available tebentafusp EAP in UK (now closed). National Coordinating Investigator for F106C Phase I study (multiple tumour types) and Principal Investigator on PRISM-301 (cutaneous melanoma), steering committee member for TebeAM (cutaneous melanoma).

APPENDIX 2: COMPANY RESPONSE TO EAP/COMMERCIAL PRODUCT QUERIES

Background: The clinical study IMCgp100-202 was closed in October 2022. Follow up data were collected for survival and subsequent treatments using a separate electronic Clinical Outcomes Assessment (eCOA) platform (YPrime Inc). With the exception of Germany, all countries permitted continued follow up after closure of the clinical trial. Unfortunately, the Germany Health Authority / Regulator did not allow follow up of patients outside the clinical trial and the remaining German patients were lost to follow due to *'sponsor ended study*'. At the time the trial was closed, in Germany 15 patients were alive and lost to follow up (12 in tebentafusp arm and 3 control arm who received pembrolizumab as investigator's choice).

1. Definition of time to treatment discontinuation (Figure 10 in the document [ID1441_company_ACD_response_Addendum 2_updated B3_v0.2 190423 ACIC]). Some people who received tebentafusp as part of the IMCgp100-202 trial as a 1st line therapy continued to receive it as part of the EAP.

Company response: In the above document, the text that refers to Figure 10 states "*In the tebentafusp PCP subgroup, 172 (86%) events out of 192 patients were observed*". The data were considered mature at the time of data cut-off on April-2022. Note, the title of the document above is different to the one we have in our records.

At the time the study closed (October 2022), 232 (97%) of 245 patients who had received tebentafusp had discontinued treatment and 181 (94%) of 192 patients from the *tebentafusp PCP subgroup* had discontinued treatment. At the time the study closed (October 2022), patients receiving tebentafusp were switched to either the EAP or commercial product, dependent on the country. Patients were not followed up for a date of discontinuation with tebentafusp because the data were considered very mature at the time the study was closed.

2. How were these people dealt with when calculating time to treatment discontinuation? Were they censored at the time they moved to EAP?

Company response: patients were censored for analysis of treatment discontinuation when the study was closed i.e. censored when they were switched to either commercial product or the EAP.

3. How was the OS dealt with in this type of patient? Were they censored at the time they moved to the EAP?

Company response: With the exception of patients in Germany, patients were followed up for survival (OS) using the eCOA platform from October 2022 (see above). Follow up for OS was independent of the EAP. After 3 years of follow up of the last patient recruited to the trial, data for the 3-year analysis was published (Hassel *et al.* 2023). Patients continue to be followed up for OS today. OS data for patients in Germany lost to follow up due to '*sponsor ended study*' were censored for analysis of OS at the time the study closed. The time points for censoring of OS for the 12 patients from the tebentafusp arm were between 27.5 and 49 months.

At the time of the 3-year analysis, 37 patients remained alive and in follow up in the tebentafusp arm of which 29 patients were in the *tebentafusp PCP subgroup*. In the control group, 11 patients remained alive, all received prior pembrolizumab as investigator's choice and 5 of the 11 received tebentafusp as a subsequent treatment.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Addendum 3: Company Response to DSU report

Company evidence submission

17th July 2024

File name	Version	Contains confidential information	Date
NICE_ID1441_ Addendum 3_ Company Response to DSUreport_17072024_redacted	**V 1**	**Yes**	**17th July 2024**

The model accompanying addendum 3 will be submitted separately Appendices J-M are included in the document Appendix K: Checklist of confidential information, will be submitted separately

TABLE OF CONTENTS

TABLES

FIGURES

Abbreviations

ACD	Appraisal Committee document
ACM	Appraisal committee meeting
AIC	Akaike information criterion
BIA	Budget impact analysis
BIC	Bayesian information criterion
BSC	best supportive care
CEAC	cost-effectiveness acceptability curve
CEM	cost-effectiveness model
CI	confidence interval
CrI	credible intervals
CRS	cytokine release syndrome
CTLA4	Cytotoxic T-lymphocyte associated protein 4
DCO	data-cut off
DSU	Decision Support Unit
EAG	External Assessment Group
ERG	External Review Group
HLA	Human leukocyte antigen
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
LYG	Life years gained
NHSE	National Health Service England
NHSE/I	National Health Service England & Ireland
NICE	National Institute for Health and Care Excellence
OS	overall survival
PAS	patient access scheme
PCP	Pre-choice pembrolizumab
PD1	Programmed cell death protein 1
PFS	progression-free survival
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life year
QOL	quality of life
RIO	rational impartial observer
SHELF	Sheffield Elicitation Framework
TTD	time to death
ULN	upper limit of normal
UM	uveal melanoma

COMPANY RESPONSE

Context

Uveal melanoma (UM) is a rare and aggressive disease. Up to 50% of patients will develop metastatic disease, after which median survival is less than 12-months [1, 2]. Until the development of tebentafusp, a novel immune-activating therapy, there had been no significant improvement in overall survival (OS) for this patient population in the last 40-years [3]. Approximately 112 patients per year in the UK with metastatic UM could be eligible for tebentafusp (NHSE BIA), addressing a high unmet clinical need for this patient population. Tebentafusp remains the only treatment with a proven survival benefit for metastatic UM. The UK clinical guidelines state that '*checkpoint inhibitors have been used a default standard of care in contemporary clinical trials; however, their activity has never been compared to placebo or no treatment*'' [4].

In the randomised controlled trial (phase 3), study IMCgp100-202, with OS as the primary endpoint, tebentafusp demonstrated a 49% reduction in the risk of death (hazard ratio (HR) 0.51 (P<0.001)) in the intention-to-treat population [5]. The study enrolled 378 patients; the largest ever conducted in this rare disease. It is the first and only licensed product for advanced uveal melanoma due to the significant improvement in OS. The UK clinical guidelines recommended that, ''*pending access and availability, clinicians consider offering tebentafusp to HLA-A*02:01 positive fit patients with metastatic disease''* [4]. Independent clinical expert advice sought by NICE found that *'tebentafusp was believed by all experts to be more effective than pembrolizumab with a difference in OS at 8-years'* [6].

To facilitate patient access to tebentafusp in the UK, the company has updated its PAS price to a reduction of [redacted]% of the list price, representing an additional reduction of [redacted] % from the previous PAS price since NICE last reviewed the appraisal. The cost per quality-adjusted life-year (QALY) of tebentafusp with the updated company base case is £[redacted] per QALY which is significantly under the £50,000 threshold for end-of-life treatment applying to this appraisal.

Background

Immunocore's response follows feedback from two appraisal committee meetings (ACMs) for the single technology appraisal ID1441, tebentafusp for HLA-A*02:01 positive patients with advanced uveal melanoma. And a subsequent (a) appeal, which was upheld on six points following a hearing on 20 October 2023; and (b) expert elicitation study for long-term survival undertaken by the NICE Decision Support Unit (DSU). The upheld appeal points related to the appeal panel's expectation that, faced with significant uncertainty, additional input from clinical experts was required to aid the committee in its review of tebentafusp. Notably, the appeal panel determined that expert clinical input should be provided on "*the most appropriate choice, and interpretation of survival curve models to interrogate the available data, and the most appropriate means of allocating supportive care costs in the model*".

NICE commissioned the NICE Decision Support Unit (DSU) (1) use a structured approach to elicit expert estimates of the expected survival of people with uveal melanoma treated with pembrolizumab and those treated with tebentafusp and the uncertainty around these estimates; and (2) consult expert opinion on the resources used in the provision of best supportive care (BSC) for people with uveal melanoma over the course of their disease after progression.

Contrary to the appeal panel's directions, NICE did not instruct the DSU to seek expert clinical input on the most appropriate choice, and interpretation of survival curve models. We also do not agree with methodology adopted by DSU, in particular exclusion of clinical experts with the most knowledge and experience managing this rare disease, and the choice of an 8-year survival estimate. Consequently, we consider some of the report's conclusions not to be clinically plausible. We reserve the right to refer to these concerns in future processes if required. However, for present purposes and in the interest of patients, we have sought to cooperatively engage with the report to hopefully enable patient access.

The Company Response to the DSU report is based on the outcome documents from this exercise – 'DSU Expert Elicitation Main Report (ID1441)' – and the two workshop reports (face-to-face and online groups).

The company response provides an updated company base case and cost-effectiveness model (CEM). Specifically, the company have updated survival assumptions consistent with feedback from clinical experts reported in the DSU report, published evidence and updated its Patient Access Scheme (PAS) price for tebentafusp. The response also includes comments on the DSU report pertinent to the revised assumptions and modelling.

Summary

The company has adopted the results for overall survival at 8-years as estimated by the clinical experts and presented in the DSU elicitation exercise reports, to update the company base case and scenarios for sensitivity analyses, thereby reducing uncertainty in the extrapolation analysis and cost-effectiveness of tebentafusp. Estimation of Best Supportive Care (BSC) costs remain unchanged. The reasons are provided the below section titled 'Company Response to DSU Expert Elicitation Methodology'. The revised base case ICER is £[redacted], which is below the cost-effectiveness threshold of £50,000 for a treatment meeting the end-of-life criterion.

Model updates relating to the appeal decision

Consistent with the appeal decision and the DSU elicitation study, the following changes to the company base case were considered:

- Extrapolation analysis of survival for both tebentafusp and pembrolizumab (comparator) based on expert clinical feedback on estimated longer-term survival at 8 years provided in the DSU reports, specifically
    - Extrapolation for OS for tebentafusp pre-choice pembrolizumab (PCP) group
    - Extrapolation for OS for pembrolizumab comparator

The choice of distributions for modelling of OS of tebentafusp PCP and pembrolizumab was updated to align with estimates of survival at 8-years in the DSU report. Modelling of costs of BSC remained unchanged, because the company approach is consistent with the feedback from the elicitation study, which stated, '"*The experts highlighted that the difference in BSC resource use would be according to patient symptomatic status […] those who are asymptomatic would be monitored for deterioration and the development of progression-associated symptoms […]*.'' The application of change in utilities relative to death in the model is also consistent with published evidence on deterioration in quality of life for other metastatic cancers [7, 8].

The impact of specific scenario analyses were also included in the cost-effectiveness model (CEM):

- a 2-year stopping rule in accordance with guidance for treatments for melanoma [9].

The updated company base case retained the data from study IMCgp100-202 (NCT03070392) (data cut date: 04 April 2022). Overlays of the OS extrapolations are provided with recent data cuts from the published 3-year analysis (data cut date June 2023) and from the most recent review of survival from April 2024 (data on file). All of the above was provided to the DSU for the elicitation study.

The PAS price for tebentafusp was updated to reflect changes in the ICER due to changes in survival assumptions to align with clinical expert opinion in the DSU report, and to comply with the end-of-life threshold of £50,000 per QALY applied to this appraisal (FAD Aug 2023 point 3.19).

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

Summary model results

The company have updated the PAS price for tebentafusp to £[redacted], which corresponds to a reduction of [redacted]% to the list price of £[redacted] and a further reduction of [redacted]% from the previous PAS (£[redacted]). The cost per quality-adjusted life-year (QALY) of tebentafusp with the updated company base case is £[redacted] per QALY.

With the new PAS, the per patient drug cost for tebentafusp is £[redacted]. Based on the NHSE/I budget impact analysis the total cost for tebentafusp is considerably below the threshold for the NHSE budget impact test.

Company Response to DSU Expert Elicitation Methodology

Introduction

The NICE appraisal committee determined that the uncertainty in modelling of OS in ACM2 was too great to recommend tebentafusp. The appeal decision required the appraisal committee to "*seek additional expert clinical input on … the most appropriate choice, and interpretation of survival curve models to interrogate the available data, and the most appropriate means of allocating supportive case costs in the model…*". NICE commissioned the DSU to perform an elicitation exercise, specifically – '*Use a structured approach to elicit expert estimates of the expected survival of people with uveal melanoma treated with pembrolizumab and those treated with tebentafusp and the uncertainty around these estimates*'. It is the company's opinion that this was not consistent with the request from the appraisal committee.

The DSU subsequently undertook an elicitation exercise to seek estimates of the proportion of patients starting treatment who would still be alive at a single time point of 8-years (number of patients out of 1,000 - termed Quantity of Interest, QoI) and uncertainty around those estimates.

Specifically:

- **QoI 1** For the pre-choice pembrolizumab (PCP) subgroup population from the IMCgp100-202 trial in the tebentafusp arm, the proportion of patients, expressed as a number per 1000, who are still alive at year 8 after randomisation.

- **QoI** 2 For the pre-choice pembrolizumab (PCP) subgroup population from the IMCgp100-202 trial in the pembrolizumab arm (excluding effect of tebentafusp as a subsequent treatment), the proportion of patients, expressed as a number per 1000, who are still alive at year 8 after randomisation.

The QoIs included the upper and lower limits of clinical plausibility, median and quartiles.

The company has several concerns and comments regarding the DSU elicitation exercise, which are detailed in the following sections:

- Methodology
    - Relevance of the SHELF method and lack of guidance on interpretation and use of the data
    - Inter-individual variation and expertise of the experts involved
    - Elicitation of survival estimates at a single time point and using a single scenario
- Face validity of the estimates given the marginal differences in the 95% credible interval between the two arms
- Impact of subsequent treatment with tebentafusp in the pembrolizumab arm in estimates of overall survival
- Best supportive care costs
- Comparison of the EAG base case with the DSU expert elicitation overall survival estimates
- Utilisation of the DSU report findings to inform the modelling assumptions in the company base case.

Methodology

Relevance of the SHELF method and lack of guidance on interpretation and use of the data

The methodology selected by the DSU for expert elicitation was the Sheffield Elicitation Framework (SHELF) v4 protocol [10]. SHELF uses behavioural aggregation, with the experts meeting together and agreeing on a final probability distribution which represents the position of a rational impartial observer (RIO) [11]. The SHELF approach required clinical experts to undergo specific training prior to participation.

No guidance was provided on how the results were to be interpreted or implemented for the appraisal of tebentafusp. In the expert elicitation main report, the DSU tabulated the findings of the face-to-face and online workshops separately with no

comment or direction on how best to ensure clinical plausibility in combining or interpreting the outputs. The results of direct feedback from the clinical experts are only included in the individual workshop reports and it is not this expert opinion that is presented as the conclusion from the workshop, the statistical analysis provided in the main report is opaque and not clearly validated for oncology medicines.

No evidence was provided by the DSU in the use of this approach for oncology and in the rare disease space. This is particularly relevant for an ultra-rare disease, such as advanced uveal melanoma. It is inevitable that, in the context of rare disease with a very small patient population, there are a limited number of experts with extensive experience treating patients and thus greater uncertainty on data and ability to predict future long-term outcomes. Indeed, previous appraisal committees have stated: ‘’*We would expect greater uncertainty in cost effectiveness and evidence should be taken as a given for such rare disease’’* [12]. The reports from the DSU elicitation exercise do not provide advice on how to implement their findings within the context of a rare disease.

Inter-individual variation and expertise of the experts involved

There is no comment on the wide variability in opinion of the experts on the 8-year survival estimates and neither on the experience of the clinical experts involved in managing advanced uveal melanoma, and particularly their experience with tebentafusp. Indeed, several of the clinicians had no direct experience of the product and only limited experience of the disease. Notably, and surprisingly, the most experienced clinicians in treating advanced uveal melanoma and tebentafusp, of which there are few due to the rarity of the disease, were excluded from the DSU study.

Elicitation of survival estimates at a single time point and using a single scenario

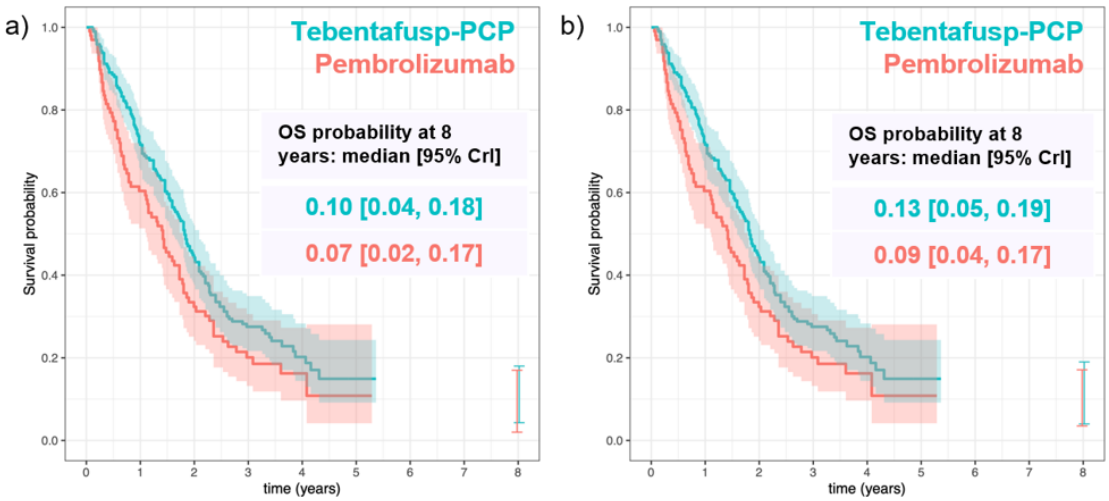
It is not stated in the reports why anchoring values to 8-year survival was chosen and how survival estimate at a single long-term time point could help reduce the uncertainty around the choice and interpretation of survival modelling. The choice of an 8-year outcome appears arbitrary.

Additionally, the experts were presented with a single scenario where the hazards remained unchanged from year 3 onwards. It was mentioned to the experts that this scenario was "*to give a point of reference for reflection on their individual judgements: no claims were made by the elicitation team regarding the probability of the scenario being true*". However, there were discussions around increasing and decreasing hazards. Hence multiple scenarios could have been presented and discussed to identify which was most clinically plausible. There was no discussion on how this specific scenario may have influenced the experts' responses and how a difference scenario may have led to alternative responses.

Face validity of the estimates given the marginal differences in the 95% credible interval between the two arms

Statistical modelling based on the DSU term Rational Impartial Observer (RIO), of the results of survival at 8-years provided directly by the clinical experts, is shown in Figure 1 (see main DSU study report). The median OS probability at 8-years and the 95% credible intervals (CrI) show that the difference between the two treatments is marginal and the overlap in the CrIs indicates that there is little, if any, difference in survival between tebentafusp and pembrolizumab. This is contrary to the feedback cited in the DSU report that "*Tebentafusp was believed by all experts to be more effective than pembrolizumab with a difference in OS at 8 years*" (DSU main report, page 9).

Figure 1. Reconstructed OS data (DCO June 2023) with the plotted RIO 95% credible interval for the a) online workshop and b) face-to-face workshop

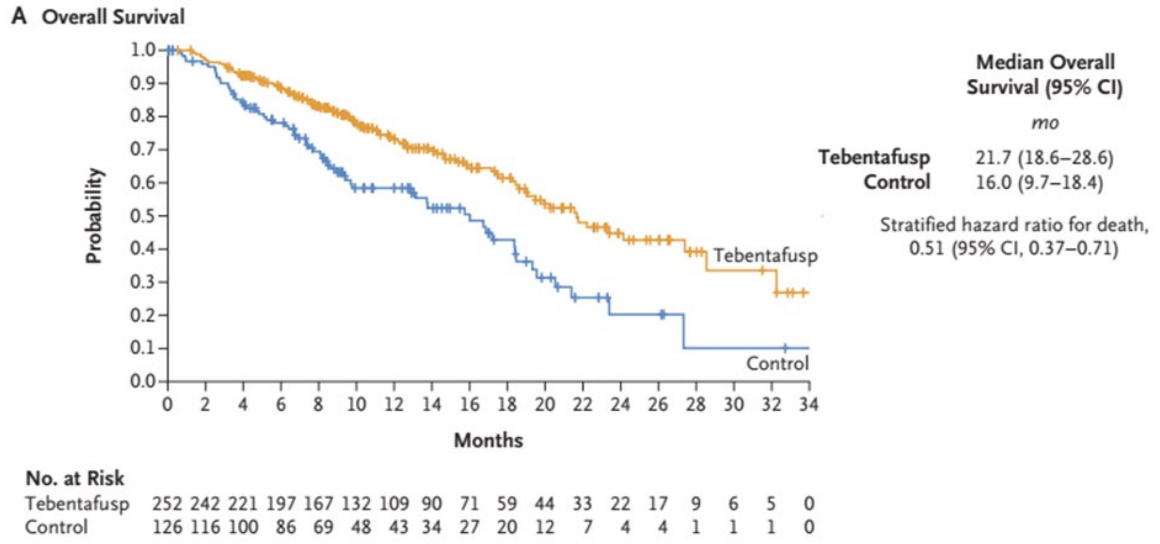


Abbreviations: RIO, Rational Impartial Observer; OS, overall survival; DCO, data cut-off; CrI, credible interval; PCP, pre-choice pembrolizumab.

In addition, the estimates provided in the DSU main report appear to differ significantly from the published primary analysis (Nathan et al.2021) and the recent 3-year analysis (Hassel et al. 2023) for study IMCgp100-202, shown below for comparison (Figure 2), which were provided in the evidence package to the DSU [5, 13].

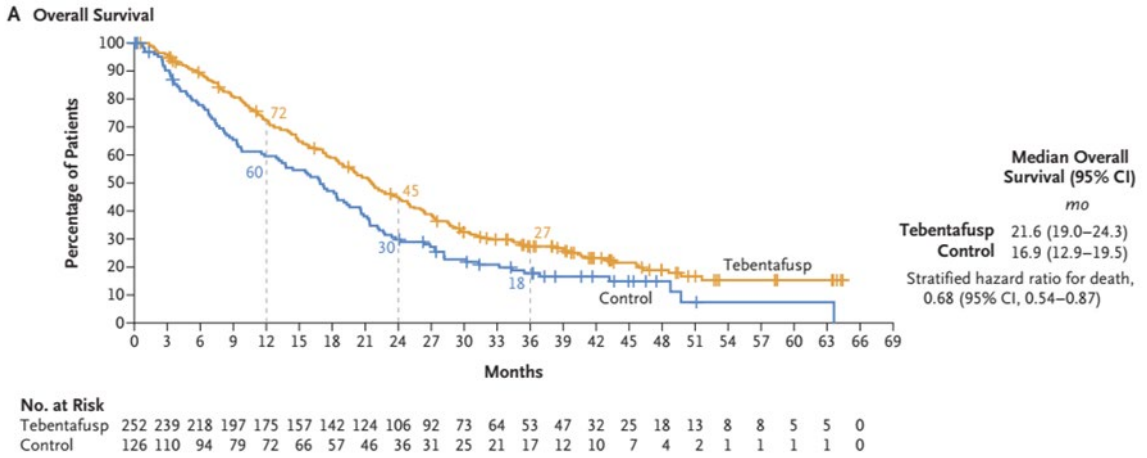
Figure 2. Overall survival in study IMCgp100-202 in (A) Primary analysis, data cut-off October 2020 and (B) 3-year analysis, data cut-off June 2023 (C) 3-year analysis for PCP tebentafusp compared to pembrolizumab.

A

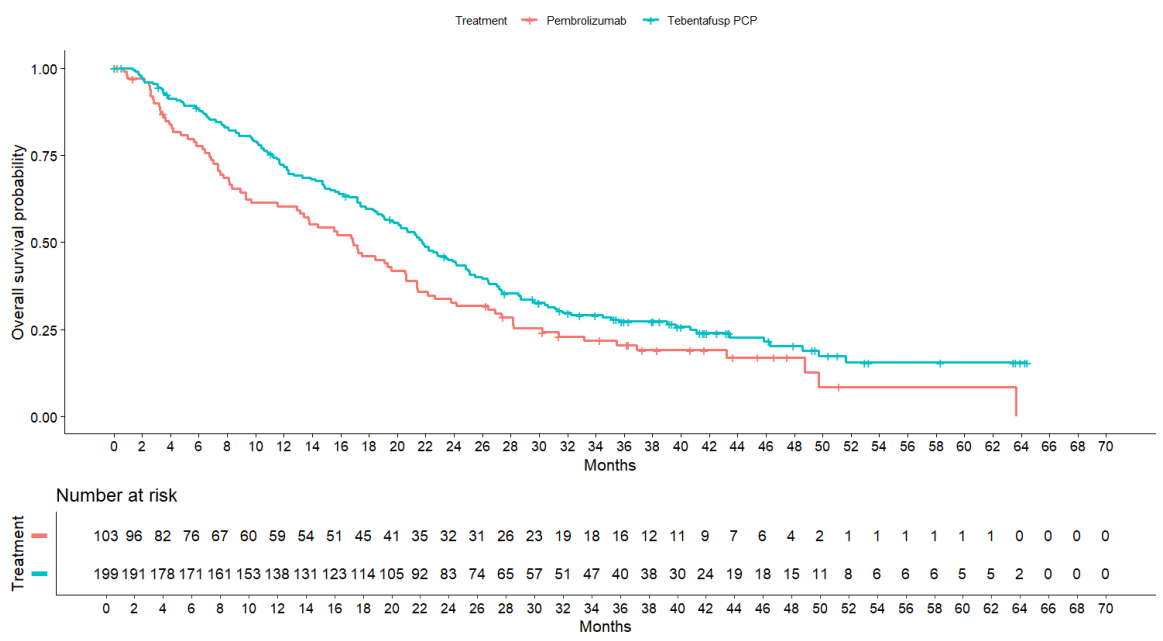


IMCgp100-202 (ITT) primary analysis, data cut-off October 2020 (Nathan et al. 2021).
Tebentafusp as a subsequent treatment was not allowed according to protocol prior to data cut-off.

B



IMCgp100-202 ITT 3-year analysis. Data cut-off June 2023 (Hassel et al., 2023). Tebentafusp as a subsequent treatment for control group (n=24) was allowed according to a protocol amendment (categorised as crossover, n=16) or outside of protocol (n=8) after primary analysis and prior to data cut-off.

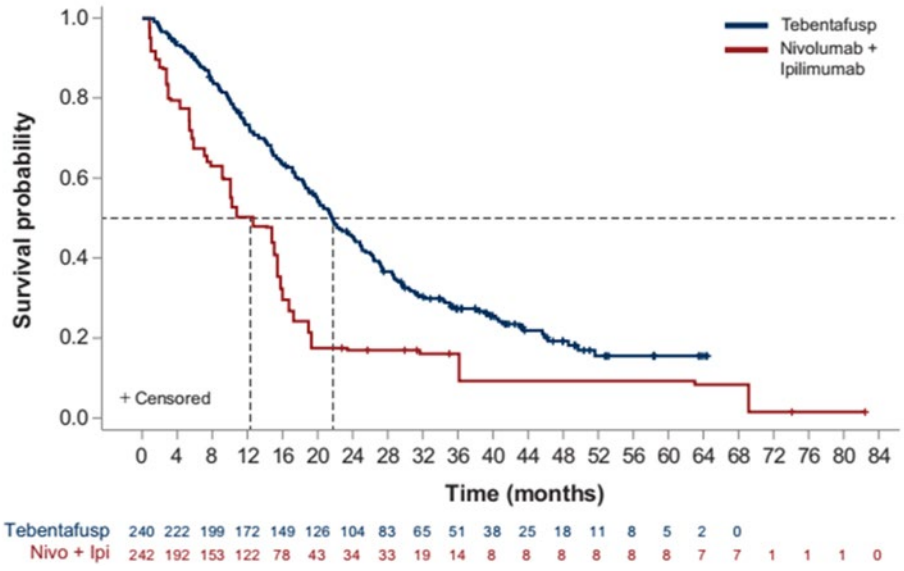


IMCgp100-202 tebentafusp (pembrolizumab pre-selected group, PCP) and pembrolizumab sub-group of control arm. Ad-hoc survival update, data cut-off June 2023 (Hassel et al., 2023).

Historical data on survival in advanced UM still reflects current outcomes (without tebentafusp) as there has been no demonstrable/significant improvement in survival from the use of immunotherapies. A superior survival benefit of tebentafusp versus investigator's choice was demonstrated in study IMCgp100-202, including versus the pembrolizumab sub-group (HR 0.51, 95% CI 0.35, 0.75) in the published primary analysis [5]. In addition the survival benefit of tebentafusp versus the combination of ipilimumab plus nivolumab, was demonstrated using an indirect comparison and analysis of individual patient level data from study IMCgp100-202 and the prospective single-arm trial GEM-1402 (NCT02626962), shown in Figure 3 [14]. Moreover, the survival with ipilimumab-nivolumab in first line metastatic uveal melanoma is no different from pembrolizumab and is consistent with published historical data in the first line setting [15, 16]. Therefore, the lack of any overall survival benefit since the availability of checkpoint inhibitors (either as monotherapy or combination) demonstrates that historical data remains valid as the most robust

evidence for the survival with advanced uveal melanoma in the absence of tebentafusp.

Figure 3. Indirect comparison of tebentafusp versus nivolumab-ipilimumab



Overall survival from tebentafusp (study IMCgp100-202) versus nivolumab plus ipilimumab (study GEM-1402) in first-line metastatic uveal melanoma: a propensity score-weighted analysis. Uses propensity scoring methods to compare tebentafusp with nivolumab-ipilimumab combination. Shows benefit in OS when treating with tebentafusp. Analysis of pembrolizumab versus nivolumab-ipilimumab showed no difference in OS (Puilats et al. 2023).

Impact of subsequent treatment with tebentafusp in the pembrolizumab arm on estimates of overall survival

Participants in the DSU survey were provided with the 3-year follow up data cut of June 2023 and the most recent OS results of April 2024 within the evidence dossier. These results include 21% (22/103) and 24% (25/103), consecutively, of the patients in the pembrolizumab arm who had received tebentafusp as a subsequent treatment. The second QoI was defined as the proportion of patients alive at 8-years for the pembrolizumab subgroup of the control arm, *"excluding effect of tebentafusp as a subsequent treatment"*. It is further reported that "*When expressing judgements for QoI 2, the experts accounted for subsequent treatments being received following pembrolizumab but excluded the potential effect of tebentafusp being received as a*

subsequent treatment." [6] However, no explanation is given as to how the experts were to account for this, whether they were provided with guidance. The DSU report did not contain any discussion on how treatment with tebentafusp as a subsequent treatment could have biased the elicitation exercise.

Several points raise concerns regarding whether the impact of subsequent treatment with tebentafusp in pembrolizumab arm in the observed data of the latest data cut-offs of study IMCgp100-202 was appropriately accounted for by the experts:

- Survival at 8-years for the pembrolizumab group reported by the DSU indicate there was minimal difference to the longest time-point of the observed KM results for OS from study IMCgp100-202 at approximately 5 years (Figure 1).

- The DSU results are inconsistent with the historical survival data, which shows 0-5% survival at 5 years [15].

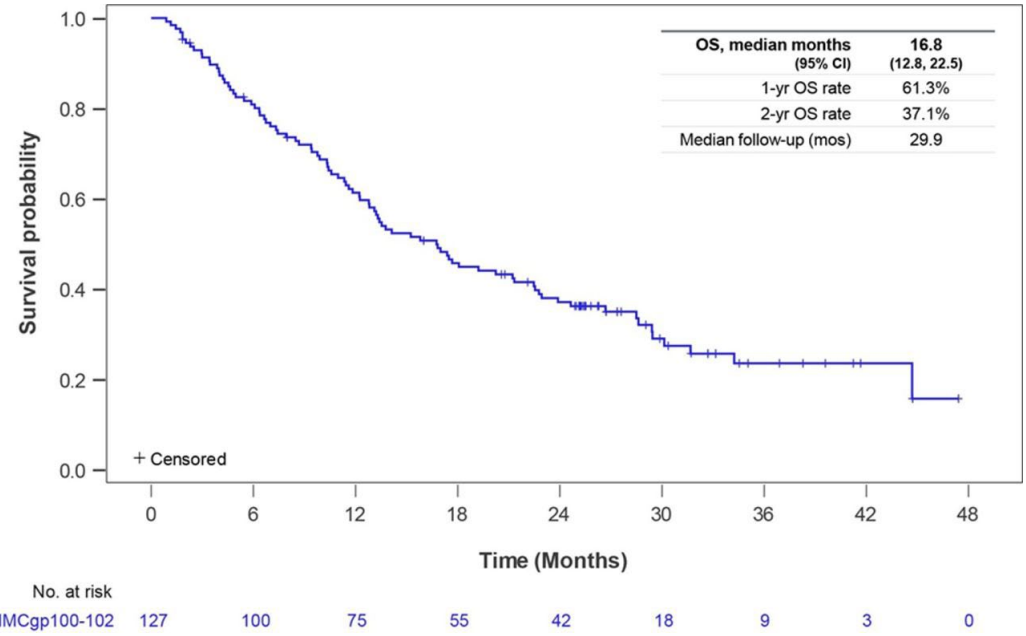
- Results from a single arm trial for tebentafusp in patients who received one or more prior therapies (study IMCgp100-102, NCT02570308) demonstrated a 1-year overall survival rate of 62% with a median overall survival of 18-months (Figure 5). This contrasts with historical 1-year overall survival in this patient population of 37% and a median overall survival of 7.8 months. This indicates that use of tebentafusp as a subsequent therapy to pembrolizumab, as was the case in study IMCgp100-202 [21% (22/103) and 24% (25/103) for the pembrolizumab group in the June 2023 and April 2024 data cuts respectively], is expected to produce significant confounding of analysis of OS of the control arm/pembrolizumab group.

- The control arm/pembrolizumab group in the most recent results (June 2023 and April 2024) do not represent current practice in the NHS, as the choice of alternative immunotherapies following treatment with pembrolizumab in the NHS is limited to ipilimumab due to the limited efficacy of re-challenge with immunotherapies [9]. This was not clearly explained to the experts.

All these elements demonstrate there is a significant risk that the survival with pembrolizumab at 8-years is significantly over-estimated in the analysis by the DSU

and does not appropriately exclude the effect of subsequent treatment with tebentafusp again calling into question the validity of this elicitation exercise for metastatic uveal melanoma.

Figure 4. Overall survival study IMCgp100-102 (Sacco *et al.,* 2022)



Impact of disease biology on long-term survival

The OS for pembrolizumab as modelled in the DSU report (Figure 1) is too high. It cannot be explained simply by patients experiencing long term survival due to disease biology, given the aggressive nature of the disease and limited survival associated with it. The DSU main report highlights the discussion among the clinical experts of "*a subgroup longer-term survivors who's biology generally results in longer survival*" for example SF3B1 mutations which are associated with a more favourable disease course [17]. However, analysis of historical data (Rantala et al. 2019) on data from a total of 2494 patients, indicates that the percent of longer-term survivors is unlikely to be above 5%; the percentage alive from the KM results for OS at 5-years is 2.7% [15].

Best supportive care costs

The second part of the elicitation exercise was to '*Consult expert opinion on the resources used in the provision of best supportive care (BSC) for people with uveal*

melanoma over the course of their disease after progression'. This exercise was completed using an online survey by 12 experts. The finding that "*The experts believed that the intensity of BSC resource use would increase in the final months of life, and that, for some patients BSC immediately after radiological progression, BSC use will be minimal due to the lack of symptoms*" The report summarises that "*the experts expressed that patient referral for BSC is an individualised decision based on patient symptoms"* and highlighted the individualised approach is based on symptomatic status which may not correlate with radiological progression.

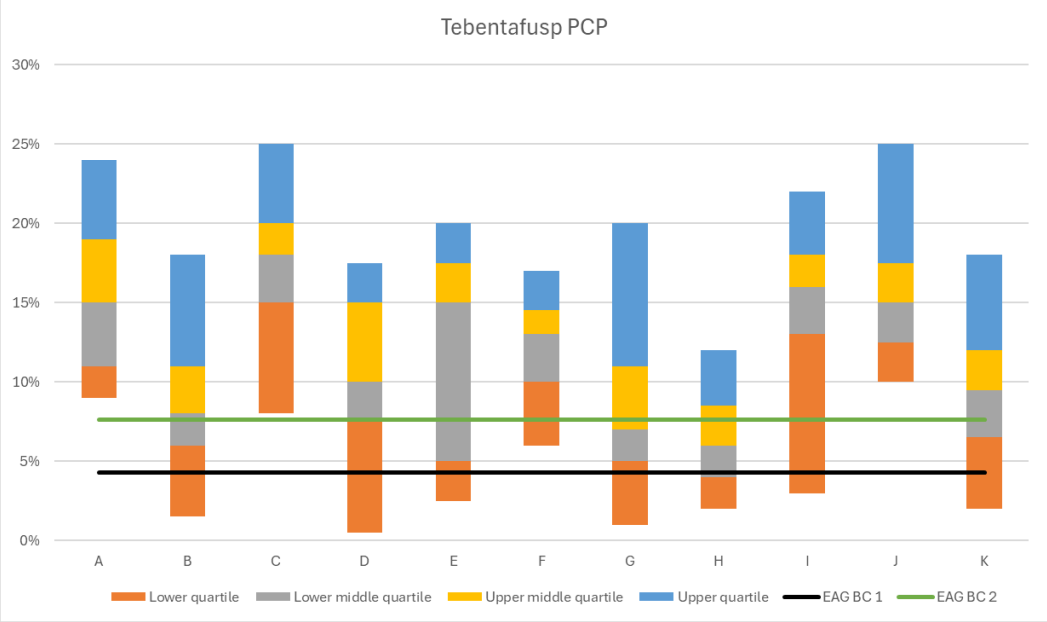
The DSU report results do not lend support to, or provide any clinical justification for, the EAG position of applying monthly costs from progression onwards. The DSU results are consistent with the BSC costing applied in the company base case in which all patients receive 4 months of BSC (a period well within the outer limits of a few weeks to 12 months provided by the clinical experts) and provide no data suggesting an alternative approach would be preferable. Hence the application of BSC costs is unchanged in the company base case.

Comparison of the EAG base case with the DSU expert elicitation overall survival estimates

Within the DSU Expert Elicitation Report, the company and EAG predicted OS probabilities at 8-years post-randomisation were presented in Table 2 of the report. In ‘base case 1’, the EAG used the generalised gamma distribution to model both arms, which gave a predicted 8-year OS probability of 4.3% in the PCP tebentafusp arm and 4.4% in the pembrolizumab arm. In ‘base case 2’, the EAG used log-logistic distribution to model both arms which gave a predicted 8-year OS probability of 7.6% in the PCP tebentafusp arm and 6.2% in the pembrolizumab arm. These predictions of lower or at best similar survival in the tebentafusp arm vs pembrolizumab do not align with the finding stated in the report that “*Tebentafusp was believed by all experts to be more effective than pembrolizumab with a difference in OS at 8-years*.'' (DSU UM Expert Elicitation Main Report, section 6.1)” [6].

Additionally, we note that the EAG ‘base case 1’ falls outside the lower plausible limit for 4 experts and for ‘base case 2’ for 3 experts and is within the lower or lower middle quartile in most other cases, as presented in Figure 5. This demonstrates that the EAG scenarios in the tebentafusp PCP group dramatically under-estimate the survival benefit of tebentafusp and highlights the importance of clinical expert input, which the EAG failed to gather to inform their choice of modelling as was noted by the Appeal panel.

Figure 5. Comparison of the EAG base cases for tebentafusp with the DSU study results



Utilisation of the DSU report findings to inform the modelling assumptions in the company base case

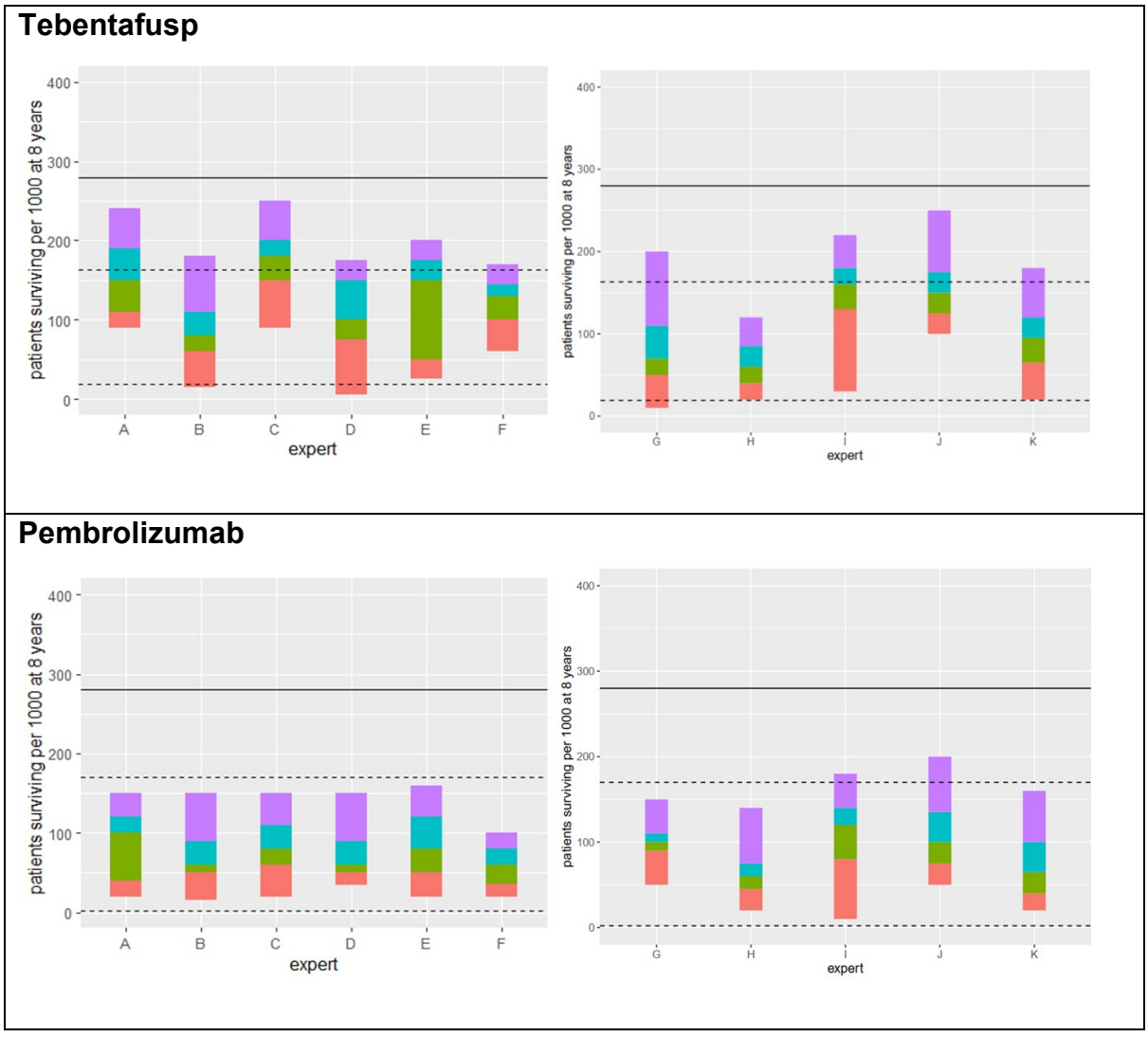
The company have used the DSU findings to ensure that the extrapolations of OS fall within the limits of clinical plausibility as established by the elicitation survey, and in line with the requirement from the appeal panel.

The DSU main report results, modelled using RIO 95% credible intervals for survival at 8 years, are inconsistent with published results demonstrating the superior survival with tebentafusp versus the control group (Investigator's choice), and overestimation of survival in the pembrolizumab arm compared to historical data which is the best evidence for comparison. Therefore, to aid transparency in the choice of survival modelling for the base case, the company adopted the results reported directly from the clinical experts, because they provide the most transparent comparison of survival analysis using the results of the elicitation study. (DSU workshop reports [18, 19]). Note, these results were not reported in the DSU main report.

Results reported directly from the clinical experts for tebentafusp and pembrolizumab are shown in Figure 4 (DSU workshop report, Section 5.2 and 6.2, respectively).

Figure 6. Individual quartile judgements for QoI 1 for tebentafusp and pembrolizumab

For each expert (online group – left, face-to-face group – right), coloured sections represent a range judged to contain the true QoI with probability 25%. Values outside the upper and lower quartiles were not judged to be clinically plausible. The solid line is the upper Kaplan-Meier 97.5% confidence limit for survival at 4 years. The dashed lines show an approximate 95% CrI for survival at 8 years that is statistically consistent with a scenario of no change in hazard from year 3 onwards (the scenario presented to the clinical experts during the elicitation exercise).



Model updates

Summary of key model updates

The company have adopted the observed data from the elicitation study provided in the workshop reports as the anchor for updates to the company's base case and scenarios and reasons are provided.

The following changes to the company base case were considered:

(i) Extrapolation for OS for tebentafusp PCP group

(ii) Extrapolation for OS for pembrolizumab comparator

The choice of distributions for modelling of OS of tebentafusp PCP and pembrolizumab was updated to align with estimates of survival at 8-years from the DSU reports. Modelling of costs of BSC remained unchanged because it was consistent with clinical expert feedback from the elicitation study and application of change in utilities relative to death in the model. This was also consistent with published evidence on deterioration in quality of life for other cancers [7].

The updated company base case retains the data from study IMCgp100-202 (NCT03070392) (data cut date: 04 April 2022). In addition, overlays of the OS extrapolations are provided with recent data cuts from the published 3-year analysis (data cut date June 2023) and from a review of survival from April 2024 (data on file provided in the DSU evidence package).

Clinical data

IMCgp100-202 dataset updates

The cost-effectiveness model submitted as part of Addendum 2 (September 2022) was based on data of study IMCgp100-202, data cut of April 2022. Since April 2022, updated results are available:

- In June 2023, representing the 3-year follow-up since the last patient randomised into the study (Hassel et al., 2023) [13],which was included in the DSU Evidence dossier used during the expert elicitation exercise and,

- The most recent data available from April 2024.

The most recent data of April 2024 is included in the model for transparency, but is not used in the analysis, because of the bias and confounding introduced by:

- High censoring in the tebentafusp group due to closure of the clinical study (Clinical data, Tebentafusp, page 26 - below).
- 24% of patients (n=25/103) who received tebentafusp as a subsequent treatment after discontinuation of pembrolizumab (Appendix M), and
- use of immunotherapy, particularly anti-PD1 therapies as a subsequent treatment following discontinuation of pembrolizumab.

Standard parametric extrapolation analysis with the June 2023 and April 2024 are reported in Appendix N for transparency and completeness.

Tebentafusp

Based on direct feedback from clinical experts in the DSU elicitation exercise, the median survival across all experts ranged between 6% and 18% for the online (A-F) and face-to-face (G-K) groups (Figure 6). The latest data cuts from study IMCgp100-202 are impacted by censoring. In the tebentafusp pre-choice pembrolizumab (PCP) group, 22 (11.1%) patients were censored or lost to follow-up, comprising: (i) withdrawn consent (n=6) and (ii) lost to follow up/sponsor ended study (n=16), which is likely to have negatively impacted the KM estimates and thus the extrapolation. Based on standard parametric extrapolation using the April 2024 data, OS at 8-years ranges from 2% to 7% which is at or below the lower end of the 95% CrI of the estimated OS at 8-years per the DSU elicitation study (Appendix N). This reinforces that this dataset is not appropriate to model the long-term survival benefit in the tebentafusp arm.

Pembrolizumab

<u>Subsequent treatment with tebentafusp after pembrolizumab in study IMCgp100-202</u>

The primary endpoint for study IMCgp100-202 (NCT03070392) was overall survival (OS). Treatment with tebentafusp post-progression in the comparator group

(Investigator's choice) was not allowed according to the protocol. Following confirmation that the study had met the primary end point (OS) at the October 2020 readout, the protocol was amended to allow crossover to tebentafusp. In addition, patients were able to receive tebentafusp as a subsequent treatment outside of the study protocol (e.g. via the company Early Access Program or commercial product) and were not categorised as '*cross-over*'.

The criteria for '*cross-over'* were defined in the amended study protocol as follows:

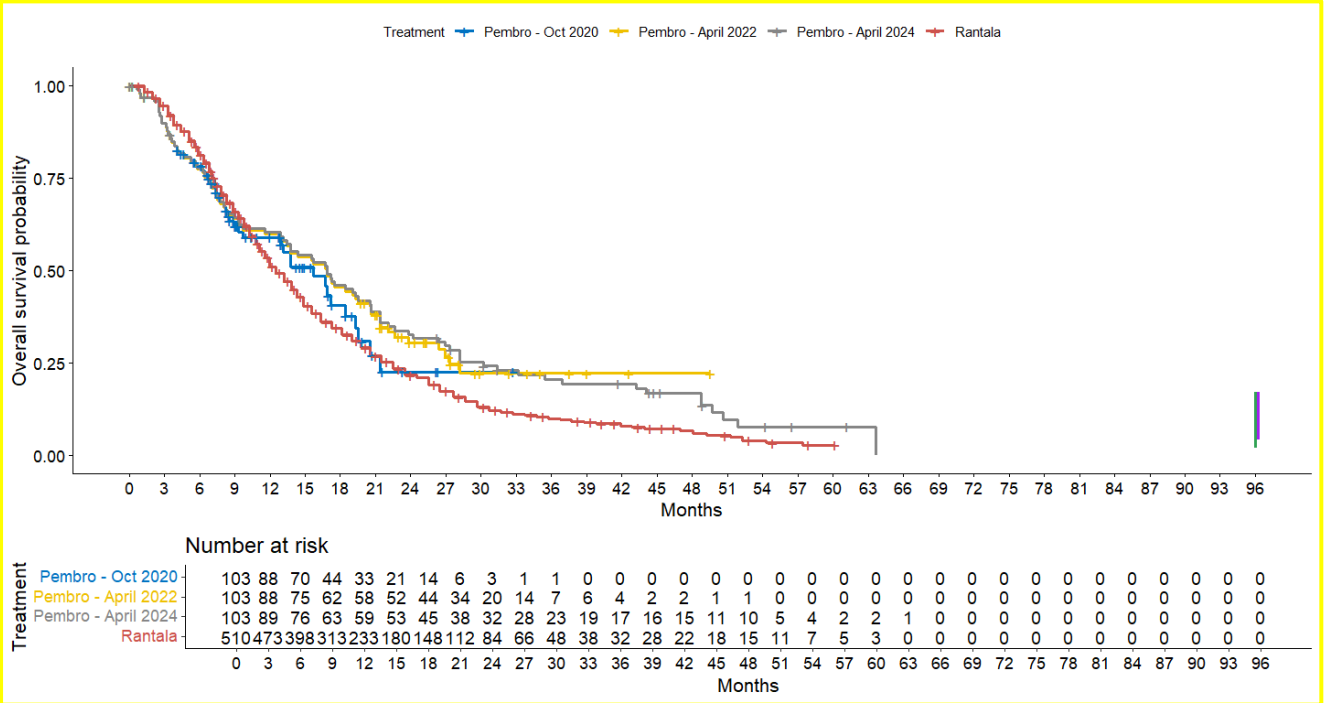
- Currently either receiving Investigator's Choice or no longer receiving study treatment but are in follow-up phase
- Provide appropriate consent prior to receiving tebentafusp
- Do not meet the treatment interruption criteria per toxicity management guidelines
- Do not have availability of tebentafusp through an alternative mechanism (e.g., Early Access Program, Named Patient Supply, or commercial supply in their location).
- Must complete a 2-week washout period for systemic anti-cancer therapy and a 4-week washout period for cytotoxic or immunotherapy agents that can present with major delayed toxicity (e.g., anti-CTLA-4) prior to receiving first dose of tebentafusp.

Sixteen patients received tebentafusp and were categorised as *'cross-over'*; two had previously been treated with ipilimumab and 14 with pembrolizumab from the investigator's choice group. These patients were included in the analysis as *'cross-over'* patients in accordance with the study protocol (Hassel et al., 2023; Hassel et al., 2023_supplementary).

After the end of the randomised treatment phase, a further 8 patients (all previously treated with pembrolizumab) were treated with tebentafusp. These patients did not fulfil the protocol criteria for crossover as they received tebentafusp via alternative mechanisms (e.g. Early Access Program, Named Patient Supply, or commercial supply in their location).

In total, 24 of 126 (19%) patients from the comparator arm received follow-up treatment with tebentafusp after the primary analysis and the published 3-year analysis (June 2023 data cut) (Table S3 – Subsequent therapies in Hassel et al., 2023_supplementary). In the group of patients that received pembrolizumab in the control arm of study IMCgp100-202, 22 of 103 (21%) received tebentafusp as a subsequent treatment (this increased to 24%, 25/103 patients, in the most recent data cut of April 2024) (Appendix M). This is likely to have significantly confounded and overestimated OS of the control group, particularly estimation of longer-term survival. Because of the study design (i.e. no clinically-defined criteria for using tebentafusp as a subsequent treatment / *'cross-over'*) and low number of patients, it was not possible to estimate the impact of tebentafusp as a subsequent treatment or provide a statistical adjustment after the primary analysis and amendment of the protocol. There are, however, clear differences between the primary analysis (Nathan et al. 2021) and most recent data cut of April 2024.

Figure 7 Overlay of overall survival in the pembrolizumab group of IMCgp100-202 for October 2020, April 2022 and April 2024 with Rantala et al. 2019



Notes: Green line, DSU elicitation online workshop 8-year OS 95% CrI 0.02-0.17; Purple line, DSU elicitation face-to-face workshop 8-year OS 95% CrI 0.04-0.17

We observe in Figure 8 that the primary analysis of October 2020 is most consistent with the historical data reported by Rantala *et al*, whereas data from analyses of longer follow-up (April 2022 and April 2024) progressively deviate after 12 months, producing a higher survival over the longer-term than historical data (20.6% in the April 2024 data cut versus 9.8% in Rantala et al 2019 at 3 years). This is undoubtedly independent of the biology of advanced uveal melanoma and related to the high number of patients that received tebentafusp as a subsequent therapy after discontinuation from pembrolizumab.

The meta-analysis provided by Rantala *et al* (2019), provides the most robust dataset for survival in advanced uveal melanoma without tebentafusp. Whilst this data incorporates different treatments, including checkpoint inhibitors such as pembrolizumab, no therapy has proven survival benefit in the last 40 years [3]. The most recent evidence for pembrolizumab [16] demonstrates that it does not improve survival in patients with advanced UM. This point was also made emphatically by the clinicians who attended the Appeal against the original final draft guidance [20]. Importantly and relevant to estimation of longer-term survival at 8-years conducted by the DSU, the analysis by Rantala *et al* indicates that the effect of disease biology in advanced uveal melanoma (e.g., SF3B1 mutation and BAP1 negative) is unlikely to produce long term survival in a sub-group of patients higher than ~5% at 8 years [1].

In the DSU elicitation exercise main report, it was highlighted that clinicians confirm that there is a “a subgroup of longer-term survivors whose biology generally results in longer survival (irrespective of treatment received)”. This is unlikely to have changed over time and so the analysis by Rantala *et al* remains the most valid data set, which indicate that survival is unlikely to be higher than 5% at 8-years.

<u>DSU elicitation study</u>

Based on direct feedback from clinical experts in the DSU elicitation exercise, the median survival across all experts ranged between 6% and 12% for the online (A-F) and face-to-face (G-K) groups (Figure 6). This is considerably higher than the OS probability of 0-5% at 5-years reported by Rantala *et al., 2019.* The inconsistency between historical data and estimates for survival with pembrolizumab at 8-years

from the DSU Main Report plus confounding of 21% of the patients who received tebentafusp as a subsequent treatment in study IMCgp100-202 have led to the company reiterating its previous estimate of 5% at 8 years. In addition, the extensive overlap of the plotted RIO 95% credible interval at 8 years for tebentafusp and pembrolizumab does not reflect the significant survival benefit of tebentafusp, HR=0.51 (95% CI 0.35 to 0.75) for pembrolizumab subgroup or HR=0.51 (95% CI 0.37 to 0.71; P<0.001) for ITT analysis.

Summary

Based on the evidence presented, the company considers:

- OS in the pembrolizumab arm of study IMCgp100-202 is significantly over-estimated in the longer follow-up data cuts, due to 21% of patients receiving tebentafusp after the primary endpoint was met.
- Tebentafusp remains the only treatment with a proven survival benefit in metastatic uveal melanoma in the last 40 years (HR point estimate of 0.51 in the primary analysis ITT).
- Estimates of OS for pembrolizumab derived in the DSU study are considerably higher than those reported by Rantala *et al*. The lack of face validity of these estimates is likely driven by the confounded OS benefits in the pembrolizumab arm in the longer follow-ups presented to the panellists due to receipt of tebentafusp and subsequent therapies. Additionally, these estimates, which were derived from the statistical derivation exercise, also contradicted statements from clinicians in the DSU reports that they believed tebentafusp demonstrates superior efficacy to pembrolizumab in metastatic UM.
- Rantala *et al*. is the most clinically robust evidence of expected survival with pembrolizumab. Longer-term survival with pembrolizumab is unlikely to be higher than 5% at 5 years.

In consideration of the above together with the clinically plausible range provided by clinical experts who participated in the DSU study, the company adopted an upper

survival benefit at 8 years of 5%. This is at, or above, the lowest plausible limit for all participants in the DSU study (Figure 6).

Figure 8. Overlay Tebentafusp PCP KM estimates April 2022, April 2024 and fitted piecewise model 26-month log-logistic

Notes: Green vertical line, DSU elicitation online workshop 8-year OS 95% CrI 0.04-0.18; Purple vertical line, DSU elicitation face-to-face workshop 8-year OS 95% CrI 0.05-0.19

Base-case distributions

The company base-case was updated (referred herein as Addendum 3) to account for the feedback received following the second committee meeting and in light of the DSU elicitation study, although the company has serious concerns regarding the validity of the exercise and therefore the estimates that were produced, as detailed in previous sections. The clinical data used to conduct the extrapolation analysis is that of April 2022 as in Addendum 2, only the chosen distributions were changed for overall survival, and are detailed in Table 1.

For the tebentafusp PCP sub-group, the piecewise modelling approach was retained, using a cut-point at 26 months and a log-logistic distribution. This gave an 8-year OS probability of 16.2%, falling in the 95%CI of the DSU elicitation study. Based on the feedback on the uncertainty in the extrapolation in the tebentafusp arm, the company adopted a cut-point at 26 months in the base case, using a larger dataset for extrapolation beyond that point.

For pembrolizumab the lognormal distribution was preferred because it is the best fitting distribution based on AIC and BIC and produced long-term OS that aligned with the DSU elicitation study, resulting in an 8-year OS probability of 5.6% compared to 0.6% in the company Addendum 2 base-case (Weibull). The company emphasises that this distribution produces a 5-year survival probability of 11.6%, which is likely conservative (i.e. comparatively high OS for pembrolizumab) given reported OS of 0-5% by Rantala *et al* [15] and clinical expert opinion.

Table 1. Distributions of OS and survival at 5-, 8-, and 10- years for the tebentafusp PCP and pembrolizumab sub-groups for the company base case

Model parameters	**Addendum 2 Modelling provided Sept 22**		**Addendum 3 Revised modelling July 24**	
Treatment	Tebentafusp PCP	Pembrolizumab	Tebentafusp PCP	Pembrolizumab
Distribution	Piecewise model 28-month, lognormal	Weibull	Piecewise model 26 months, loglogistic	Lognormal
5-year OS	23.4%	5.0%	21.2%	11.6%
8-year OS	19.9%	0.6%	16.2%	5.6%
10-year OS	18.5%	0.2%	14.3%	3.8%

Note: Grey shading denotes outside of clinical plausible range reported in DSU study.

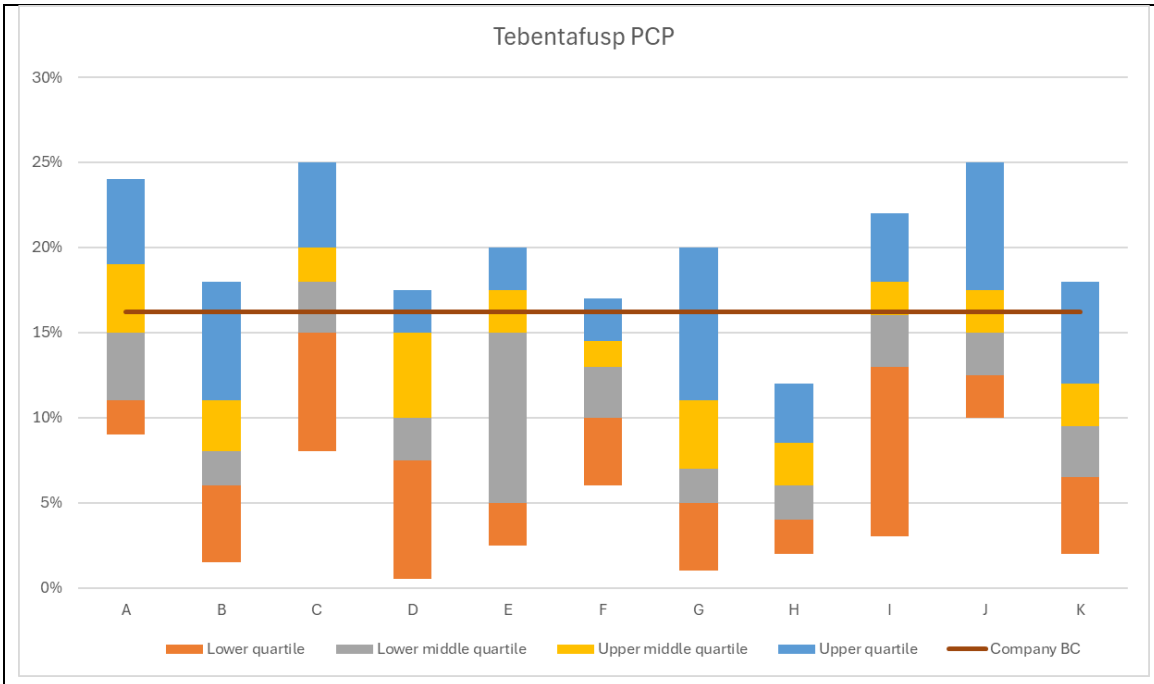
Figure 6 shows the 8-year survival estimates for tebentafusp PCP and pembrolizumab overlaid with the feedback of the upper and lower limits, and quartiles of clinical plausibility reported by each of the clinical experts in the DSU elicitation exercise.

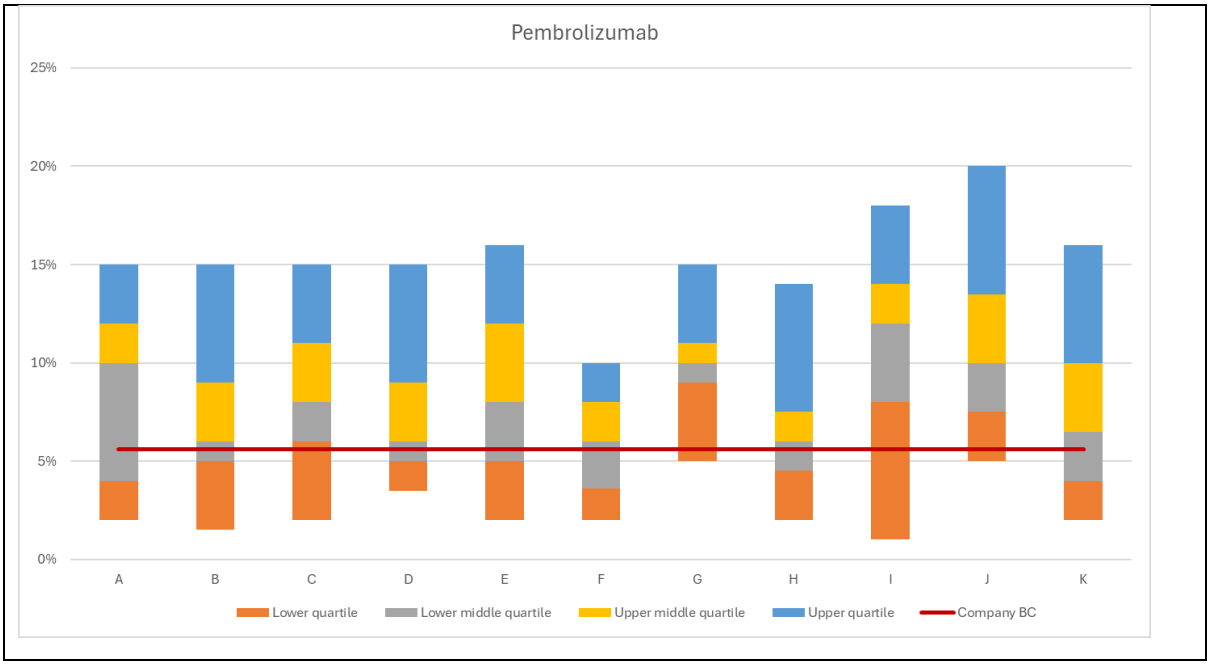
In summary, the 8-year survival in the company base case for tebentafusp PCP is 16.2%, which is comfortably within the upper range of clinical plausibility with exception of a single exception (expert H). Of note, expert H reported a greater upper quartile in the pembrolizumab arm (140/1000) than in the tebentafusp arm (120/1000), which is inconsistent with the statement that "*Tebentafusp was believed by all experts to be more effective than pembrolizumab with a difference in OS at 8-years*." (DSU UM Expert Elicitation Main Report, section 6.1). The median survival at 8 years across all experts ranged between 6% to 18% for the online (A-F) and face-to-face (G-K) groups. The modelling approach for the base case was selected

to take account of the likely effect of censoring of the tebentafusp group due to closure of the study.

In summary, the 8-year survival in the company base case for pembrolizumab is 5.6%. Selection of modelling of OS for pembrolizumab was guided by: (1) comparison with historical data (Rantala *et al*. 2019), (2) consideration of likely longer-term survivors linked to favourable disease biology, (3) consideration of the beneficial effect of tebentafusp as a subsequent treatment in 25 of the 103 patients (24%) after pembrolizumab in the April 2024 data cut and (4) lower quartile for clinical plausibility reported by the clinical experts in the DSU study. From the individual results reported by the clinical experts, 5% survival for 9 of 11 experts is within the lower or lower middle quartile of clinical plausibility and the remaining 2 experts reported 5% survival as the lower limit of clinical plausibility. Taken together (1-4 above), 5.6% survival for pembrolizumab at 8-years is a reasonable estimate.

Figure 9 Overlay of clinical experts' responses in the DSU study and OS modelled in the company base case, (A) Tebentafusp PCP, (B) Pembrolizumab





Other model updates

Base case

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] reduced to £[redacted] with PAS.

Other economic modelling parameters

Remaining parameters were retained unchanged from the updated company base case of Addendum 2 submitted on 30 September 2022. Details of the changes made in Addendum 1, and Addendum 2 to the company base-case are presented in and Appendix L: model updates from Addendum 2 (30 September 2022) retained in Addendum 3 (11 July 2024).

Scenario analysis

Tebentafusp stopping rule

Consistent with NICE's guideline on melanoma and the recent recommendation of nivolumab–relatlimab (Opdualag) for the treatment of metastatic melanoma (NICE TA950), including for advanced uveal melanoma, stopping immunotherapies after 2-years of treatment is considered routine clinical practice. This was informed by clinical experts and the Cancer Drug Fund representative, and it was accepted by the Committee that a 2-year stopping rule is part of commissioning practice, which in the case of TA950, included treatment for advanced uveal melanoma.

Tebentafusp is administered intravenously on a weekly basis. It is not expected that patients would be on treatment for longer than 24-months in routine practice and it is anticipated that the clinical benefit will extend beyond the duration of treatment. This approach is consistent with the 2-year stopping rule used in a NICE appraisal of nivolumab–relatlimab (TA950).

The company has adopted a 2-year stopping rule in the scenario analysis consistent with the previous assessment of the immunotherapy (TA950). In the model, treatment discontinuation is applied at 2-years, beyond which no drug acquisition nor administration costs are accrued in both the tebentafusp arm and the pembrolizumab arm.

Cost-effectiveness model results

Base case

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 2. Base-case results.

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] vs. [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 2. Base-case results) and the probabilistic sensitivity analysis (PSA) ICER was £[redacted] per QALY (Table 3. Results of the base-case PSA).

Table 2. 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								

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 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 11). 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 12.

Table 3 presents the mean incremental costs and QALYs as well as the ICER as estimated in the base-case PSA.

Table 3. 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 10. Cost-effectiveness plane – incremental costs vs. incremental QALYs

[redacted]

Figure 11. 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 13 and the corresponding ICERs for the upper and lower estimates for each parameter are shown in Table 4.

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, which remained below £50,000/QALY.

Figure 12. Tornado diagram

Table 4. 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]
Overnight hospital stay (338.11, 563.51)	[redacted]	[redacted]
Proportion female (0.37, 0.62)	[redacted]	[redacted]
Health states costs End-of life care (one-off) (one year) (9405.00, 15675.00)	[redacted]	[redacted]
Data from the literature Time to death in days ≥360 days (0.74, 0.90)	[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]

Scenario analyses

The impact of a choice of parameters were further explored through a number of scenario analyses:

- Inclusion of a 2-year stopping rule in both arms of the model, in line with NICE guidance on melanoma and TA950, results presented in Table 5.

- Weibull, exponential and Gompertz distribution in the pembrolizumab arm to align long-term OS with the data reported by Rantala *et al* and clinical expert opinion received by the company and noted in the ACD following ACM1 "*The clinical experts explained that the overall survival estimates from the company's model were plausible*" [21]: results are presented in Table 6.

- Weibull and log-normal distribution for OS in the tebentafusp PCP arm, alternative distribution consistent with the estimates of the DSU elicitation study: results presented in Table 6.

Table 5. Results of scenario analyses on treatment duration

Scenario	**ICER (£/QALY)**	**% change**
Base-case	[redacted]	NA
2-year stopping rule in both treatment arms	[redacted]	[redacted]

Table 6. Results of scenario analysis on overall survival distributions

Parameter	Base-case		Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
Treatment	Tebentafusp PCP	Pembrolizumab	Pembrolizumab	Pembrolizumab	Pembrolizumab	Tebentafusp PCP	Tebentafusp PCP
Distribution	Piecewise model 26 months + log-logistic	Lognormal	Exponential	Weibull	Gompertz	Piecewise model 26 months + Weibull	Piecewise model 26 months + Log-normal
5-year OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8-year OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10-year OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% change			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: Grey shading denotes outside of clinical plausible range reported in DSU study.

B.4 References

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B.5 Appendices

Appendix K: Checklist of confidential information

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

Appendix L: model updates from Addendum 2 (30 September 2022) retained in Addendum 3 (11 July 2024)

Clinical data

Extrapolation analysis based on the April 2022 data cut off of study IMCgp100-202.

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), 42.4% of the patients treated with tebentafusp had an interruption at any time, with a mean duration of 22.2 days, and 18 patients (7.3%) 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. That means up to four weeks a year or a compliance of 92% (48/52). The majority of treatment interruptions in the trial were less than two weeks (72%). Treatment restart was typically in the outpatient setting (95%), without dose modification from most recent dose (98%) or steroid premedication (98%). Grade 2 cytokine release syndrome (CRS) was uncommon at restart and occurred mostly in patients with preceding grade 2 CRS [22].

Treatment interruption in the pembrolizumab arm was limited (16.5%), most patients didn’t have an interruption or a dose reduction (83.5%).

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 7.

- 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 the Addendum B2 (section extrapolation analysis, overall survival), 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 Addendum B2 (section Extrapolation analysis, overall survival) the hazard of the pembrolizumab and tebentafusp arm are distinct (Figure 7, Addendum B2, section Extrapolation analysis, overall survival), 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., 2019.

A stepwise implementation of the ERG preferred scenario is presented in Table 7, and demonstrates that the increase in the ICER is driven by then choice of OS in the tebentafusp arm. A stepwise implementation of the ERG preferred scenario is presented in Table 7, and demonstrates that the increase in the ICER is driven by then choice of OS in the tebentafusp arm.

Table 7. Results of scenario analyses using ERG preferred scenarios

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

Table 8. Stepwise implementation of the ERG preferred scenario

Scenario	ICER (£/QALY)	% change
Base-case (APR2022 DCO) Piecewise-28, log-normal (tebentafusp PCP) 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]

Appendix M: IMCgp100-202 subsequent therapy report summary

Table 9 shows subsequent treatments that patients received in study IMCgp100-202, some patients received multiple subsequent therapies captured in the attached table. A total of 25 patients from the pembrolizumab sub-group of the Investigator's Choice arm received tebentafusp (IMCgp100) as a subsequent treatment following pembrolizumab as of April 2024.

In addition, a large proportion of patients received a subsequent immunotherapy (CTLA4, PD1, PD1/other) other than tebentafusp. During ACM2 for this appraisal, a committee member noted that the guidance for melanoma did not recommend for a second immunotherapy if a patient has received a prior immunotherapy.

Table 9: Summary of subsequent therapies in intent-to-treat population study IMCgp100-202 April 2024 data cut

Subsequent Therapy	Tebentafusp (N=252)	Dacarbazine (N=7)	Ipilimumab (N=16)	Pembrolizumab (N=103)	Investigator's Choice (N=126)	Overall (N=378)
Systemic	151 (59.9)	3 (42.9)	9 (56.3)	64 (62.1)	76 (60.3)	227 (60.1)
Chemotherapy	45 (17.9)	2 (28.6)	2 (12.5)	14 (13.6)	18 (14.3)	63 (16.7)
Immunotherapy	133 (52.8)	3 (42.9)	6 (37.5)	52 (50.5)	61 (48.4)	194 (51.3)
CTLA4	87 (34.5)	0	3 (18.8)	27 (26.2)	30 (23.8)	117 (31.0)
PD1	119 (47.2)	3 (42.9)	3 (18.8)	32 (31.1)	38 (30.2)	157 (41.5)
PD1/Other	1 (0.4)	0	0	2 (1.9)	2 (1.6)	3 (0.8)
Other immunotherapies	19 (7.5)	0	2 (12.5)	26 (25.2)	28 (22.2)	47 (12.4)
IMCgp100	0	0	2 (12.5)	25 (24.3)	27 (21.4)	27 (7.1)
Other	19 (7.5)	0	0	4 (3.9)	4 (3.2)	23 (6.1)
Other systemic therapies	4 (1.6)	0	0	2 (1.9)	2 (1.6)	6 (1.6)
Targeted	20 (7.9)	2 (28.6)	1 (6.3)	11 (10.7)	14 (11.1)	34 (9.0)
Local therapy	27 (10.7)	0	7 (43.8)	15 (14.6)	22 (17.5)	49 (13.0)
Radiotherapy	35 (13.9)	1 (14.3)	4 (25.0)	19 (18.4)	24 (19.0)	59 (15.6)
Surgery	1 (0.4)	0	0	1 (1.0)	1 (0.8)	2 (0.5)
Other therapies	4 (1.6)	0	0	2 (1.9)	2 (1.6)	6 (1.6)

Appendix N: Extrapolation analysis April 2022, June 2023 and April 2024

The extrapolation analysis conducted to inform the choice of modelling for the company base case are presented below. Table 10 presents the piecewise model fitted in the tebentafusp PCP arm and the standard parametric models fitted in the pembrolizumab arm using the April 2022 data cut. Table 11 and Table 12 present the standard parametric extrapolation models fitted in both the tebentafusp PCP and pembrolizumab arm using the June 2023 and April 2024 data cuts. Extrapolation analyses were conducted with these two datasets for completeness and transparency, however, they were not used in the cost-effectiveness model because of the bias and confounding introduced by:

- high censoring in the tebentafusp group due to closure of the clinical study (Clinical data, Tebentafusp, page 26).
- 24% patients (n=25/103) who received tebentafusp as a subsequent treatment after discontinuation of pembrolizumab as of April 2024(Appendix M), and
- use of immunotherapy, particularly anti-PD1 therapies as a subsequent treatment following discontinuation of pembrolizumab (Appendix M).

Table 10. Extrapolation analysis April 2022 data cut off tebentafusp pre-choice pembrolizumab and pembrolizumab

Months	KM April 2022 DC	Rantala et al 2019	Company base case PW 26-month (Log-logistic)	PW 26 month Exponential	PW 26 month Weibull	PW 26 month Lognormal	PW 26 month Log-logistic	PW 26 month Gompertz	PW 26 month Generalised gamma
TEBENTAFUSP PCP									
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]
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBROLIZUMAB									
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]
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Based on individual ranking for AIC and BIC, multiple distributions may have the same overall ranking

Table 11. Extrapolation analysis June 2023 data cut off tebentafusp pre-choice pembrolizumab and pembrolizumab

Months	KM April 2022 DC)	Rantala et al 2019	Company base case	Exponential	Weibull	Lognormal	Log-logistic	Gompertz	Generalised gamma
TEBENTAFUSP PCP									
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]
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBROLIZUMAB									
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]
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Based on individual ranking for AIC and BIC, multiple distributions may have the same overall ranking

Table 12. Extrapolation analysis April 2024 data cut off tebentafusp pre-choice pembrolizumab and pembrolizumab

Months	KM April 2024 DC	Rantala et al 2019	Company base case	Exponential	Weibull	Lognormal	Log-logistic	Gompertz	Generalised gamma
TEBENTAFUSP PCP									
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]
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBROLIZUMAB									
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]
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Based on individual ranking for AIC and BIC, multiple distributions may have the same overall ranking

1. Clinical effectiveness

1.1 Trial data available during original submission

The updated company base case retained the data from study IMCgp100-202 (NCT03070392) (data cut date: 04 April 2022). Overlays of the OS extrapolations are provided with recent data cuts from the published 3-year analysis (data cut date June 2023) and from the most recent review of survival from April 2024 (data on file). The company argued that the original data with a data cut of 04 April 2022 provided a more accurate representation of the treatment effect of tebentafusp versus investigator choice (IC) for two main reasons:

- High censoring in the tebentafusp group due to closure of the clinical study.

"The latest data cuts from study IMCgp100-202 are impacted by censoring. In the tebentafusp pre-choice pembrolizumab (PCP) group, 22 (11.1%) patients were censored or lost to follow-up, comprising: (i) withdrawn consent (n=6) and (ii) lost to follow up/sponsor ended study (n=16), which is likely to have negatively impacted the KM estimates and thus the extrapolation." (p. 26)

The company then compare clinical expert estimates of OS from the DSU elicitation exercise with those from standard parametric extrapolation of the April 2024 data at 8 years: 6 to 18% vs. 2 to 7%.

- 24 (19%) patients in the IC arm subsequently received tebentafusp.

"Because of the study design (i.e. no clinically-defined criteria for using tebentafusp as a subsequent treatment / 'cross-over') and low number of patients, it was not possible to estimate the impact of tebentafusp as a subsequent treatment or provide a statistical adjustment after the primary analysis and amendment of the protocol." (p. 28)

The company then in overlays of the OS K-M curves for pembrolizumab compare the data cuts for October 2020, April 2022, April 2024 and the meta-analysis by Rantala et al. 2019. They state: *"We observe in Figure 8 that the primary analysis of October 2020 is most consistent with the historical data reported by Rantala et al, whereas data from analyses of longer follow-up (April 2022 and April 2024) progressively deviate after 12 months, producing a higher survival over the longer-term than historical data (20.6% in the April 2024 data cut versus 9.8% in Rantala et al 2019 at 3 years)."* (p. 29) They argue that Rantala et al 2019 "…provides the most robust dataset for survival in advanced uveal melanoma without tebentafusp." They also cite a study by Rossi et al. 2019 as evidence that pembrolizumab does not improve survival in patients with advanced uveal melanoma.

EAG comment

It does seem likely that censoring and crossover in the tebentafusp and IC arms respectively is likely to affect the estimation of the treatment effect of tebentafusp vs. IC.

However, it is unclear what the direction of the effect on the tebentafusp arm is. It must also be noted that clinical expert opinion of long-term survival for at treatment that is not yet standard clinical practice must be regarded with caution. Therefore, the latest data cut for tebentafusp might still have value at least in a scenario of the cost effectiveness analysis.

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were only 17 patients in this study and median OS was not reached. Also, the authors commented that: *"The small number of patients responding to pembrolizumab showed a remarkable survival advantage."* (p.1184) The EAG would therefore recommend that an attempt be made to adjust for the crossover despite the data limitations.

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)
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- 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 [redacted] for tebentafusp only, this was increased to [redacted] for IC
  - The proportion of subsequent treatment with nivolumab monotherapy was reduced to [redacted] for tebentafusp only (this was [redacted] for IC, as in the CS base-case)
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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: [redacted]).
  - 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

Compared with the CS addendum 2, CS addendum 3 did include updates for:

- OS
    - Assuming piecewise model for tebentafusp (Kaplan-Meier + log-logistic distribution for extrapolation; cut-off point: [redacted]).
    - Assuming a log-normal distribution for IC (pembrolizumab)
- Tebentafusp treatment costs
    - Updated tebentafusp PAS [redacted].

2.1.1 Reproducing company's updated base-case

The EAG used the ACM 2 company base-case (deterministic ICER: [redacted], model file: "NICE_ID 1441_IMCR_12092022_CONFIDENTIAL_CIC_300922.xlsm") to reproduce the company's updated base-case by implementing the changes highlighted above. Notably, the EAG could not exactly reproduce the updated base-case ICER of [redacted] reported by the company. The ICER obtained by the EAG was [redacted], indicating a difference of £4. Similarly, when the EAG used the most recent model and attempted to revert to the ACM 2 company base-case, the ICER obtained was [redacted] (not [redacted]), again indicating a difference of £4. It is unclear to the EAG what the cause of this minor difference is.

2.2 EAG comments

2.2.1 Overall survival

In the DSU main report on the expert elicitation exercise, it was stated that:

- "*All experts were hesitant to suggest a cure potential due to the limited data.*"
- "*The online group's RIO median and 95% credible interval for OS probability is 0.10 (0.04, 0.19) for the tebentafusp arm and 0.07 (0.02, 0.17) for the pembrolizumab arm. The face-to-face group's RIO median and 95% credible interval is 0.13 (0.05, 0.19) for the tebentafusp arm and 0.09 (0.04, 0.17) for the pembrolizumab arm.*"

These results, combined with the 8-year OS predictions are presented in Table 2.1. Note that the EAG added the incremental results given these are generally the predominant drivers of the incremental results (including the ICER). Additionally, it is unclear to the EAG why the DSU did select the 8-year point for the expert elicitation instead of alternative time points, or even multiple time points (as also highlighted by the company).

Table 2.1. Comparison of OS survival at 8 years.

	Precited 8-year OS probability (PCP)		
	Tebentafusp	**Pembrolizumab**	**Increment**
DSU (online expert elicitation)	0.100 (CI: 0.040-0.019)	0.070 (CI: 0.020-0.170)	0.030
DSU (face-to-face expert elicitation)	0.130 (CI: 0.05-0.019)	0.090 (CI: 0.040-0.170)	0.040
Company - ACM 2[a]	[redacted]	[redacted]	[redacted]
EAG (generalised gamma) - ACM 2	[redacted]	[redacted]	[redacted]
EAG (log-logistic) - ACM 2	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	
Company - post appeal[b]	[redacted]	[redacted]	[redacted]
EAG - post appeal scenario 1[c]	[redacted]	[redacted]	[redacted]
EAG - post appeal scenario 1[d]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, 95% credible interval

[a] Tebentafusp: Kaplan-Meier + log-normal distribution for extrapolation; cut-off point: [redacted], pembrolizumab: Weibull distribution

[b] Tebentafusp: Kaplan-Meier + log-logistic distribution for extrapolation; cut-off point: [redacted], pembrolizumab: log-normal distribution

[c] Tebentafusp and pembrolizumab: log-normal distribution

[d] Tebentafusp: log-logistic distribution, pembrolizumab: generalised Gamma distribution

In CS addendum 3, the company updated the base-case distribution to account for the feedback received on the second committee meeting and DSU elicitation study. The updated company base-case used the data from study IMCgp100-202 with the April 2022 data cut (similarly as the CS base-case submitted for ACM2), i.e. the data from April 2024 were not used to parameterise the economic model. The company did not provide a comprehensive assessment systematically considering the appropriateness of different (standard) approaches to estimate OS (similarly for PFS and TTD submitted for ACM 2). Therefore, the EAG does not find compelling evidence to deviate from most of 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. Nonetheless, the EAG has added suggestions for alternative plausible scenarios regarding OS extrapolation based on the results of the DSU elicitation study.

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, as discussed in the committee meeting and appeal letter. 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). In fact, in the post-appeal letter, the panel highlighted that Rantala et al. 2019, had included very few patients receiving pembrolizumab and the majority of those patients treated with checkpoint inhibitor immunotherapy agents (such as pembrolizumab) that were included in this study, were doing so as second-line treatment. 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. 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 [redacted] patients were at risk at 36 months for tebentafusp and pembrolizumab respectively, while this is [redacted] at 48 months, see CS addendum 2 Figure 1) and; iii) the [redacted] of QALY gains are accumulated beyond the observed data period (CS addendum 2 Table 8).

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 3 Figure 9, seemingly resulting in a plateau. In fact, from 16 years onwards in the model, patients taking tebentafusp had the same death rate as the general population, which implies they are "cured". Notably, the DSU report stated that all experts were hesitant to suggest a cure potential due to the limited data. 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.

As shown in Table 2.1, the company´s base-case after the post-appeal assumed the OS of tebentafusp and pembrolizumab to be on the higher and lower end of the CI, respectively. Hence, the difference in 8-year OS does not seems plausible and/or in line with the DSU expert elicitation results. Specifically, the increment between the median expected average between tebentafusp and pembrolizumab ([redacted]) is notably higher than the one estimated from the expert elicitation results (0.030 and 0.040).

After considering the clinical evidence provided by the NICE DSU expert elicitation study, the EAG considered that the log-logistic distribution is a plausible approximation for the OS of tebentafusp and pembrolizumab. The log-logistic 8-year OS probabilities (Table 2.1) were slightly lower than the median predicted by the clinical experts in both tebentafusp and pembrolizumab and with a lower increment ([redacted]) than those obtained in the elicitation study (0.030 and 0.040). Moreover, the EAG proposes two additional scenario analyses to further explore the impact of alternative OS extrapolations. Firstly, a log-normal distribution was selected for both arms (i.e., tebentafusp and pembrolizumab), which reported 8-year OS estimates that felt within the limits of clinical plausibility (tebentafusp: [redacted], pembrolizumab: [redacted]), in line with the requirements of the appeal and with an increment that aligned more closely with the one from the clinical elicitation study (Table 2.1). Secondly, a log-logistic curve was selected for tebentafusp (8-year OS: [redacted]) and a generalised gamma was selected for pembrolizumab (8-year OS: [redacted]), which led to an increment of [redacted]. The estimates of this scenario are also in line with the evidence provided by the NICE DSU expert elicitation study (Table 2.1)

2.2.2 BSC costs

In the DSU main report the company's and EAG position on BSC costs were summarised:

- "*The company based their approach on the study by McKendrick et al. 2016, where BSC is shown to be provided for an average of 4 months for patients with metastatic melanoma. Based on this, the entire cohort of patients within the trial is assumed to receive BSC for an average of 4 months. Within the model, the costs associated with BSC are applied as a one-off cost at the point of progression of patients. This approach applies the one-off 4-month BSC cost to all progressed patients, irrespective of how long they then spend within the progressed state. The company also include end-of-life costs to reflect the additional management of patients within the final year of life.*"
- "*The EAG believed that costs associated with BSC would be dependent on the time between progression and death and therefore opted to apply BSC costs monthly to reflect this. In response to company concerns of double-counting of end-of-life costs through the implementation of monthly BSC costs, the EAG removed end-of-life costs from the model.*"

However, the survey described in the DSU report does not really address the appropriateness of these perspectives, i.e. whether BSC costs would be dependent on the time between progression and death. The survey covered the following questions:

- Would patients start receiving BSC when they have progressed, irrespective of the level of deterioration in their quality of life?
- Would the sub-population of longer-term survivors be receiving BSC after progression?
- Would the rest of the population (i.e. non-long-term survivors) receive BSC after progression?

However, the DSU report included statements that supported the EAG preferred assumption that BSC costs are dependent on the time between progression and death:

- "*A range of durations of BSC were provided by the experts, spanning a few weeks to twelve months.*"

- "*To summarise, the experts expressed that patient referral for BSC is an individualised decision based on patient symptoms. Even fit and well patients who have not yet deteriorated, may be referred to palliative care units to start planning later support. All patients will continue to have regular reviews in order to monitor their disease progression irrespective of their level of deterioration.*"
- "*Patients who exhibit symptoms associated with progression would require palliative care and further monitoring, whereas those who are asymptomatic would be monitored for deterioration and the development of progression-associated symptoms but otherwise may not receive other aspects of BSC. Some experts did highlight that all patients (irrespective of their symptomatic status) would be referred to community palliative care units to start building relationships and planning long-term care regimes.*"

Moreover, individual responses indicated that BSC would be initiated at the point of progression and would be until death.

- "*It is likely that those with progression would need ongoing BSC until death from disease or the development of a suitable treatment for them*"
- "*BSC initiated at the point of progression and duration would be for the anticipated life expectancy (median 9-12 months)*"

Given the above, as well as the arguments provided in section 4.2.9 of the original EAG report, the EAG would prefer incorporating 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).

2.2.3 Treatment and administration costs

The EAG wanted to highlight outstanding issues from CS Addendum 2: 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 [redacted] 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 [redacted] were unclear to the EAG (based on Addendum 2 Appendix L the EAG could not reproduce this estimate). 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, [redacted] with pembrolizumab required a dose interruption, with a mean duration of [redacted] days. Hence the EAG, would recommend a consistent approach, either 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, only including 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 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. This justification should also include why the estimated subsequent therapies are different for patients that initially received tebentafusp and pembrolizumab.

2.3 EAG proposed analyses

The EAG would propose the following analyses:

- Standard parametric survival approach for both comparators for PFS and TTD using the generalised Gamma distribution (no piecewise approach)
- Alternative OS approaches to estimate long-term OS:
    - Using standard parametric distributions
        - Log-logistic for both treatments
        - Log-normal for both treatments
        - log-logistic distribution for tebentafusp and generalised Gamma distribution for pembrolizumab
    - Exploring scenarios incorporating alternative assumptions regarding treatment effect waning
- Incorporating monthly BSC costs per cycle in the PD health state while removing end of life costs to prevent potential double counting
- Consistent approach to including adherence correction for calculation treatment acquisition costs
- Incorporating administration costs using National Cost Collection data, i.e. consistent with the original CS
- Justification and potential alternative assumptions related to the subsequent therapies following discontinuation of the active treatment

1. Clinical effectiveness

1.1 Trial data available during original submission

The updated company base case retained the data from study IMCgp100-202 (NCT03070392) (data cut date: 04 April 2022). Overlays of the OS extrapolations are provided with recent data cuts from the published 3-year analysis (data cut date June 2023) and from the most recent review of survival from April 2024 (data on file). The company argued that the original data with a data cut of 04 April 2022 provided a more accurate representation of the treatment effect of tebentafusp versus investigator choice (IC) for two main reasons:

- High censoring in the tebentafusp group due to closure of the clinical study.

"The latest data cuts from study IMCgp100-202 are impacted by censoring. In the tebentafusp pre-choice pembrolizumab (PCP) group, 22 (11.1%) patients were censored or lost to follow-up, comprising: (i) withdrawn consent (n=6) and (ii) lost to follow up/sponsor ended study (n=16), which is likely to have negatively impacted the KM estimates and thus the extrapolation." (p. 26)

The company then compare clinical expert estimates of OS from the DSU elicitation exercise with those from standard parametric extrapolation of the April 2024 data at 8 years: 6 to 18% vs. 2 to 7%.

- 24 (19%) patients in the IC arm subsequently received tebentafusp.

"Because of the study design (i.e. no clinically-defined criteria for using tebentafusp as a subsequent treatment / 'cross-over') and low number of patients, it was not possible to estimate the impact of tebentafusp as a subsequent treatment or provide a statistical adjustment after the primary analysis and amendment of the protocol." (p. 28)

The company then in overlays of the OS K-M curves for pembrolizumab compare the data cuts for October 2020, April 2022, April 2024 and the meta-analysis by Rantala et al. 2019. They state: *"We observe in Figure 8 that the primary analysis of October 2020 is most consistent with the historical data reported by Rantala et al, whereas data from analyses of longer follow-up (April 2022 and April 2024) progressively deviate after 12 months, producing a higher survival over the longer-term than historical data (20.6% in the April 2024 data cut versus 9.8% in Rantala et al 2019 at 3 years)."* (p. 29) They argue that Rantala et al 2019 "…provides the most robust dataset for survival in advanced uveal melanoma without tebentafusp." They also cite a study by Rossi et al. 2019 as evidence that pembrolizumab does not improve survival in patients with advanced uveal melanoma.

EAG comment

It does seem likely that censoring and crossover in the tebentafusp and IC arms respectively is likely to affect the estimation of the treatment effect of tebentafusp vs. IC.

However, it is unclear what the direction of the effect on the tebentafusp arm is. It must also be noted that clinical expert opinion of long-term survival for at treatment that is not yet standard clinical practice must be regarded with caution. Therefore, the latest data cut for tebentafusp might still have value at least in a scenario of the cost effectiveness analysis.

On the other hand, it does seem most likely that crossover to tebentafusp would increase survival. However, the EAG still consider that the Rantala et al. 2019 data are limited by differences in treatment mix with the IC arm. Indeed, Rossi et a. 2019 cannot be regarded as convincing evidence that pembrolizumab is not superior to treatments in the Rantala et al. 2019 meta-analysis given that there

were only 17 patients in this study and median OS was not reached. Also, the authors commented that: *"The small number of patients responding to pembrolizumab showed a remarkable survival advantage."* (p.1184) The EAG would therefore recommend that an attempt be made to adjust for the crossover despite the data limitations.

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- 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
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  - The proportion of subsequent treatment with pembrolizumab was increased to [redacted] for tebentafusp only (this was [redacted] 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: [redacted]).
  - 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

Compared with the CS addendum 2, CS addendum 3 did include updates for:

- OS
    - Assuming piecewise model for tebentafusp (Kaplan-Meier + log-logistic distribution for extrapolation; cut-off point: [redacted]).
    - Assuming a log-normal distribution for IC (pembrolizumab)
- Tebentafusp treatment costs
    - Updated tebentafusp PAS [redacted].

2.1.1 Reproducing company's updated base-case

The EAG used the ACM 2 company base-case (deterministic ICER: [redacted], model file: "NICE_ID 1441_IMCR_12092022_CONFIDENTIAL_CIC_300922.xlsm") to reproduce the company's updated base-case by implementing the changes highlighted above. Notably, the EAG could not exactly reproduce the updated base-case ICER of [redacted] reported by the company. The ICER obtained by the EAG was [redacted], indicating a difference of £4. Similarly, when the EAG used the most recent model and attempted to revert to the ACM 2 company base-case, the ICER obtained was [redacted] (not [redacted]), again indicating a difference of £4. It is unclear to the EAG what the cause of this minor difference is.

2.2 EAG comments

2.2.1 Overall survival

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- "*All experts were hesitant to suggest a cure potential due to the limited data.*"
- "*The online group's RIO median and 95% credible interval for OS probability is 0.10 (0.04, 0.19) for the tebentafusp arm and 0.07 (0.02, 0.17) for the pembrolizumab arm. The face-to-face group's RIO median and 95% credible interval is 0.13 (0.05, 0.19) for the tebentafusp arm and 0.09 (0.04, 0.17) for the pembrolizumab arm.*"

These results, combined with the 8-year OS predictions are presented in Table 2.1. Note that the EAG added the incremental results given these are generally the predominant drivers of the incremental results (including the ICER). Additionally, it is unclear to the EAG why the DSU did select the 8-year point for the expert elicitation instead of alternative time points, or even multiple time points (as also highlighted by the company).

Table 2.1. Comparison of OS survival at 8 years.

	Precited 8-year OS probability (PCP)		
	Tebentafusp	**Pembrolizumab**	**Increment**
DSU (online expert elicitation)	0.100 (CI: 0.040-0.019)	0.070 (CI: 0.020-0.170)	0.030
DSU (face-to-face expert elicitation)	0.130 (CI: 0.05-0.019)	0.090 (CI: 0.040-0.170)	0.040
Company - ACM 2[a]	[redacted]	[redacted]	[redacted]
EAG (generalised gamma) - ACM 2	[redacted]	[redacted]	[redacted]
EAG (log-logistic) - ACM 2	[redacted]	[redacted]	[redacted]
Company - post appeal[b]	[redacted]	[redacted]	[redacted]
EAG - post appeal scenario 1[c]	[redacted]	[redacted]	[redacted]
EAG - post appeal scenario 1[d]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, 95% credible interval

[a] Tebentafusp: Kaplan-Meier + log-normal distribution for extrapolation; cut-off point: [redacted], pembrolizumab: Weibull distribution

[b] Tebentafusp: Kaplan-Meier + log-logistic distribution for extrapolation; cut-off point: [redacted], pembrolizumab: log-normal distribution

[c] Tebentafusp and pembrolizumab: log-normal distribution

[d] Tebentafusp: log-logistic distribution, pembrolizumab: generalised Gamma distribution

In CS addendum 3, the company updated the base-case distribution to account for the feedback received on the second committee meeting and DSU elicitation study. The updated company base-case used the data from study IMCgp100-202 with the April 2022 data cut (similarly as the CS base-case submitted for ACM2), i.e. the data from April 2024 were not used to parameterise the economic model. The company did not provide a comprehensive assessment systematically considering the appropriateness of different (standard) approaches to estimate OS (similarly for PFS and TTD submitted for ACM 2). Therefore, the EAG does not find compelling evidence to deviate from most of 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. Nonetheless, the EAG has added suggestions for alternative plausible scenarios regarding OS extrapolation based on the results of the DSU elicitation study.

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, as discussed in the committee meeting and appeal letter. 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). In fact, in the post-appeal letter, the panel highlighted that Rantala et al. 2019, had included very few patients receiving pembrolizumab and the majority of those patients treated with checkpoint inhibitor immunotherapy agents (such as pembrolizumab) that were included in this study, were doing so as second-line treatment. 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. 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 [redacted] patients were at risk at 36 months for tebentafusp and pembrolizumab respectively, while this is [redacted] at 48 months, see CS addendum 2 Figure 1) and; iii) the [redacted] of QALY gains are accumulated beyond the observed data period (CS addendum 2 Table 8).

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 3 Figure 9, seemingly resulting in a plateau. In fact, from 16 years onwards in the model, patients taking tebentafusp had the same death rate as the general population, which implies they are "cured". Notably, the DSU report stated that all experts were hesitant to suggest a cure potential due to the limited data. 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.

As shown in Table 2.1, the company´s base-case after the post-appeal assumed the OS of tebentafusp and pembrolizumab to be on the higher and lower end of the CI, respectively. Hence, the difference in 8-year OS does not seems plausible and/or in line with the DSU expert elicitation results. Specifically, the increment between the median expected average between tebentafusp and pembrolizumab ([redacted]) is notably higher than the one estimated from the expert elicitation results (0.030 and 0.040).

After considering the clinical evidence provided by the NICE DSU expert elicitation study, the EAG considered that the log-logistic distribution is a plausible approximation for the OS of tebentafusp and pembrolizumab. The log-logistic 8-year OS probabilities (Table 2.1) were slightly lower than the median predicted by the clinical experts in both tebentafusp and pembrolizumab and with a lower increment ([redacted]) than those obtained in the elicitation study (0.030 and 0.040). Moreover, the EAG proposes two additional scenario analyses to further explore the impact of alternative OS extrapolations. Firstly, a log-normal distribution was selected for both arms (i.e., tebentafusp and pembrolizumab), which reported 8-year OS estimates that felt within the limits of clinical plausibility (tebentafusp: [redacted], pembrolizumab: [redacted]), in line with the requirements of the appeal and with an increment that aligned more closely with the one from the clinical elicitation study (Table 2.1). Secondly, a log-logistic curve was selected for tebentafusp (8-year OS: [redacted]) and a generalised gamma was selected for pembrolizumab (8-year OS: [redacted]), which led to an increment of [redacted]. The estimates of this scenario are also in line with the evidence provided by the NICE DSU expert elicitation study (Table 2.1)

2.2.2 BSC costs

In the DSU main report the company's and EAG position on BSC costs were summarised:

- "*The company based their approach on the study by McKendrick et al. 2016, where BSC is shown to be provided for an average of 4 months for patients with metastatic melanoma. Based on this, the entire cohort of patients within the trial is assumed to receive BSC for an average of 4 months. Within the model, the costs associated with BSC are applied as a one-off cost at the point of progression of patients. This approach applies the one-off 4-month BSC cost to all progressed patients, irrespective of how long they then spend within the progressed state. The company also include end-of-life costs to reflect the additional management of patients within the final year of life.*"
- "*The EAG believed that costs associated with BSC would be dependent on the time between progression and death and therefore opted to apply BSC costs monthly to reflect this. In response to company concerns of double-counting of end-of-life costs through the implementation of monthly BSC costs, the EAG removed end-of-life costs from the model.*"

However, the survey described in the DSU report does not really address the appropriateness of these perspectives, i.e. whether BSC costs would be dependent on the time between progression and death. The survey covered the following questions:

- Would patients start receiving BSC when they have progressed, irrespective of the level of deterioration in their quality of life?
- Would the sub-population of longer-term survivors be receiving BSC after progression?
- Would the rest of the population (i.e. non-long-term survivors) receive BSC after progression?

However, the DSU report included statements that supported the EAG preferred assumption that BSC costs are dependent on the time between progression and death:

- "*A range of durations of BSC were provided by the experts, spanning a few weeks to twelve months.*"

- "*To summarise, the experts expressed that patient referral for BSC is an individualised decision based on patient symptoms. Even fit and well patients who have not yet deteriorated, may be referred to palliative care units to start planning later support. All patients will continue to have regular reviews in order to monitor their disease progression irrespective of their level of deterioration.*"
- "*Patients who exhibit symptoms associated with progression would require palliative care and further monitoring, whereas those who are asymptomatic would be monitored for deterioration and the development of progression-associated symptoms but otherwise may not receive other aspects of BSC. Some experts did highlight that all patients (irrespective of their symptomatic status) would be referred to community palliative care units to start building relationships and planning long-term care regimes.*"

Moreover, individual responses indicated that BSC would be initiated at the point of progression and would be until death.

- "*It is likely that those with progression would need ongoing BSC until death from disease or the development of a suitable treatment for them*"
- "*BSC initiated at the point of progression and duration would be for the anticipated life expectancy (median 9-12 months)*"

Given the above, as well as the arguments provided in section 4.2.9 of the original EAG report, the EAG would prefer incorporating 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).

2.2.3 Treatment and administration costs

The EAG wanted to highlight outstanding issues from CS Addendum 2: 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 [redacted] 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 [redacted] were unclear to the EAG (based on Addendum 2 Appendix L the EAG could not reproduce this estimate). 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, [redacted] with pembrolizumab required a dose interruption, with a mean duration of [redacted] days. Hence the EAG, would recommend a consistent approach, either 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, only including 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 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. This justification should also include why the estimated subsequent therapies are different for patients that initially received tebentafusp and pembrolizumab.

2.3 EAG proposed analyses

The EAG would propose the following analyses:

- Standard parametric survival approach for both comparators for PFS and TTD using the generalised Gamma distribution (no piecewise approach)
- Alternative OS approaches to estimate long-term OS:
    - Using standard parametric distributions
        - Log-logistic for both treatments
        - Log-normal for both treatments
        - log-logistic distribution for tebentafusp and generalised Gamma distribution for pembrolizumab
    - Exploring scenarios incorporating alternative assumptions regarding treatment effect waning
- Incorporating monthly BSC costs per cycle in the PD health state while removing end of life costs to prevent potential double counting
- Consistent approach to including adherence correction for calculation treatment acquisition costs
- Incorporating administration costs using National Cost Collection data, i.e. consistent with the original CS
- Justification and potential alternative assumptions related to the subsequent therapies following discontinuation of the active treatment

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

Post appeal – deadline for comments 5pm on 31 July 2024. Please submit via NICE Docs.

	As a stakeholder you are invited to provide the committee with your comments on the DSU report that was produced in response to the upheld appeal points for this appraisal. If you have any further comments that you believe are relevant to the committee discussion following the appeal, please include them in this form. We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline. Deadline for comments by **5pm** on **31 July 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).
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.	[**n/a**]
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We thank the committee for attempting to elicit further expert opinion.
2	The exercise focused on an opinion on extrapolation of the KM curves from the 202 study. Although additional datasets are mentioned in the report there was not however a focus or discussion regarding the relevance of these in interpreting the performance of both arms in the 202 study. Specifically, whether the performance of the control arm and the extrapolations of it reflect historical

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	data and whether cross-over of patients from the experimental to the control arm had an impact on control arm performance.
3	The selection of 8 years as a landmark is curious as the level of uncertainty at this time point will be so significant given the lack of precedent with this new class of agent. We would like to understand why a 5 year landmark not chosen as an initial landmark of focus?
4	Metastatic Uveal Melanoma is a rare disease and the majority of melanoma oncologists have very limited experience of both the disease and tebentafusp. The tebentafusp registration study was only run at two sites in England – Mount Vernon and Clatterbridge. The expanded access program, enabling wider access to tebentafusp, opened at 17 sites in the UK. However, 52% of the treated patients were at just 3 sites – Clatterbridge, Mount Vernon and The Royal Marsden. It will be in the committee's interest in enabling the highest quality assessment to ensure that at the next appraisal meeting expert opinion is garnered from those clinicians with greatest experience of the drug and disease. There are areas (above) that were not the focus of the elicitation exercise that expert opinion could help the committee with.
5	
6	

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- 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):	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]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are pleased steps have been taken to understand the impact that Tebentafusp has had on people who had access to this treatment. It is unfortunate that Clinical Nurse Specialists (CNSs) were unable to share their valuable experience in supporting patients with uveal melanoma. We seek clarity on the information shared during their contact and whether more could have been done to stress their unique experience was needed to understand the care needs of patients with uveal melanoma. We are concerned that CNSs may not have engaged with the exercise if they felt

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	they did not have the experience to contribute to the modelling workshop.
2	We are also unclear whether the nominating party could have supplied an alternate email address for the 10 undeliverable emails so that more people's views could have been included.
3	Given the lack of data on uveal melanoma, we believe it is crucial for the committee to fully understand the impact Tebentafusp has made so that an informed decision can be made. Our appeal has centred on the costs associated with Best Supportive Care (BSC) as we know so many people living and living well with this cancer, which we haven't seen before. We engage with patients from diagnosis through progression and symptom management, as well as with their loved ones after their passing, which provides us with a good understanding of how transformative this treatment has been. Best Supportive Care is a broad term, and we felt questions could have been clearer, which was a sentiment shared by several respondents. We believe the varied responses reflect the ambiguity in question phrasing. For instance, it is unclear how a respondent should address question 1 if patients are referred to BSC upon progression without symptoms and do not engage with services until symptoms appear.
4	We feel more questions could have been asked to understand the 'resources used in the provision of best supportive care for people with uveal melanoma throughout their disease after progression'. Following the results from this survey and the literature review, we worry the committee will still be unclear on what supportive care looks like for people with uveal melanoma. With some cancers, there is a general understanding of the conditions it could cause, eg. lymphoedema, but this doesn't seem true for people with uveal melanoma. This is a rare cancer, so it is vital clinical experts are used to their fullest for costs to be accurately predicted. If it's agreed this area could be better understood, we would welcome an exercise to be held with CNSs and Clinicians to explore areas with limited published data and leverage the expertise of clinical specialists to bridge these gaps.
5	
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Clinical expert statement

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

[redacted]

My personal statement is as follows:

I am a medical oncologist by training, and am employed as a reader at the University and as an honorary consultant at the Clatterbridge Cancer Centre. My specialist interest is in melanoma with a particular clinical and research focus on uveal melanoma (UM). Clatterbridge Cancer Centre has historically been the only centre providing proton beam radiotherapy for UM, while our partner hospital, the Royal Liverpool Hospital, is one of only three specialist centres for UM treatment. Our practice is thus one of the largest in the country, underpinning our involvement in key clinical research in the field. This includes national academic research such as the recent SUAVE (led by my colleague Ernie Marshall) and SelPac (for which I was co-CI and translational lead). In addition I was local PI for both tebentafusp UM trials and a member of the international steering group for both. I have additionally contributed towards the FOCUS trial which led to FDA licencing of PHP, and was lead recruiting centre for the novel agent RP2 in UM (which is now being explored in a phase III study). I am also local PI of two studies from Ideaya (as one of only 3 centres in the UK) and will further be involved in the ATOM EORTC adjuvant study (again with only 3 centres). Our centre also enrolled very strongly to the tebentafusp EAP, extending my clinical experience in the field.