NICE National Institute for Health and Care Excellence

NICE guidance

Tebentafusp for treating advanced uveal melanoma

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendation 4

2 Information about tebentafusp 5

Marketing authorisation indication 5

Dosage in the marketing authorisation 5

Price 5

3 Committee discussion 6

Treatment pathway 6

Tebentafusp 7

Generalisability of the clinical evidence 8

Clinical evidence results 10

The economic model 12

Survival modelling 12

Appeal outcome 13

Assumptions in the economic model 18

End of life 23

Acceptable incremental cost-effectiveness ratio 23

Cost effectiveness 24

Innovation 25

Equality issues 25

Conclusion 26

4 Implementation 27

5 Evaluation committee members and NICE project team 28

Evaluation committee members 28

Chair 28

NICE project team 28

1 Recommendation

1.1 Tebentafusp is recommended, within its marketing authorisation, for treating HLA-A*02:01-positive unresectable or metastatic uveal melanoma in adults. Tebentafusp is only recommended if the company provides it according to the commercial arrangement.

Why the committee made this recommendation

There is no standard treatment specifically for HLA-A*02:01-positive unresectable or metastatic (advanced) uveal melanoma. Usually people are offered immunotherapies normally used for treating cutaneous melanoma, such as pembrolizumab, or chemotherapy. Tebentafusp aims to treat the specific features of HLA-A*02:01-positive uveal melanoma.

Clinical trial evidence suggests that tebentafusp could increase how long people live and how long they have before their cancer gets worse compared with usual treatment.

Tebentafusp meets the criteria for a life-extending treatment at the end of life and is likely to increase how long people live. Accounting for uncertainty, the cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, tebentafusp is recommended.

2 Information about tebentafusp

Marketing authorisation indication

2.1 Tebentafusp (Kimmtrak, Immunocore) is indicated 'as monotherapy for the treatment of human leukocyte antigen (HLA)-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for tebentafusp.

Price

2.3 The list price for tebentafusp (200 micrograms per 1-ml vial) is £10,114 (BNF online accessed September 2024).

2.4 The company has a commercial arrangement. This makes tebentafusp available to the NHS with a discount. The size of the discount is commercial in confidence.

3 Committee discussion

The appraisal committee considered evidence submitted by Immunocore, a review of this submission by the evidence review group (ERG), and responses from stakeholders. Following an upheld appeal, further evidence was commissioned from the NICE Decision Support Unit (DSU) and the company updated its model. See the committee papers for full details of the evidence.

This technology appraisal was done using NICE's guide to the methods of technology appraisal 2013.

Treatment pathway

Tebentafusp would be a welcome new treatment option

3.1 The patient experts explained that uveal melanoma is a rare and aggressive disease with a poor prognosis. They explained that around 50% of people diagnosed with the condition will develop metastases. So, many people with uveal melanoma live with the fear that they will be diagnosed with advanced disease. This is made more distressing by the prospect that once the cancer has metastasised, life expectancy is usually short. There are few treatment options for advanced disease, and those that are available have limited effect (see section 3.2). The patient experts explained that symptoms may not affect a person's quality of life until the late stages of the disease. But the psychological burden of waiting for 6-monthly scans is immense, because a finding on a scan could mean prognosis suddenly worsens. People want treatments that could potentially decrease tumour burden and increase overall survival. The patient experts explained that having tebentafusp as a treatment option would bring significant hope to people with uveal melanoma, including people with localised disease who fear metastatic disease. The committee heard from the patient experts that having treatment with tebentafusp meant that people with the condition had more time to live a relatively normal life. The committee concluded that there is an unmet need for people in this disease area, which has very limited effective treatment options. Tebentafusp would be a welcome treatment option.

There is no standard care for advanced uveal melanoma

3.2 The patient and clinical experts explained that there is no standard care for advanced uveal melanoma. The clinical experts explained that the treatments used are those licensed for melanoma. These include pembrolizumab, nivolumab and ipilimumab immunotherapies, and dacarbazine chemotherapy. Most people with advanced uveal melanoma are offered pembrolizumab, and some people are offered ipilimumab with or without nivolumab. A small minority of people who cannot have immunotherapies are offered dacarbazine. The clinical experts explained that uveal melanoma is biologically distinct from cutaneous melanoma, and that there is no evidence for the effectiveness of immunotherapies for treating uveal melanoma. A clinical expert noted that the nivolumab and ipilimumab combination has a higher toxicity profile than pembrolizumab or ipilimumab, so it is not used as often as other immunotherapies. They also explained that nivolumab monotherapy is not used in clinical practice because people find the dosing schedule of pembrolizumab more convenient. The committee concluded that although pembrolizumab is the most common treatment option, there is no standard care for advanced uveal melanoma.

Tebentafusp

Tebentafusp is a new drug with a novel mechanism of action

3.3 The clinical experts explained that tebentafusp is a new drug that works differently to checkpoint inhibitors such as pembrolizumab, ipilimumab and nivolumab, and other immunotherapies used to treat cancer. Tebentafusp acts as a molecular bridge to link cancer cells to T cells in a person's immune system. This bridge is formed through an interaction between tebentafusp and a protein called gp100, which is almost always found on the surface of uveal melanoma cells. Tebentafusp binds to CD3 on T cells, forms a synapse with the gp100 peptide-HLA complex and destroys the cancer cells. The clinical experts explained that any cancer cell with gp100 proteins could potentially be targeted by tebentafusp, including cutaneous melanoma. But uveal melanoma is particularly susceptible because its tumour cells have a particularly high amount of gp100 proteins. The committee concluded that tebentafusp is a new drug with

a novel mechanism of action.

Tebentafusp would be used primarily as a first-line treatment for advanced uveal melanoma in line with the IMCgp100-202 trial

3.4 IMCgp100-202 is an open-label randomised controlled trial investigating the effectiveness of tebentafusp as a first-line treatment for advanced uveal melanoma (n=378). IMCgp100-102 is a single-arm trial of tebentafusp for treating advanced uveal melanoma in people who have had 1 or more lines of treatment for advanced disease (n=146). The clinical experts noted that tebentafusp would be used primarily as a first-line treatment based on evidence from IMCgp100-202. But they noted that the results from IMCgp100-102 showed the potential clinical benefit of tebentafusp as a second-line treatment for advanced disease. So, the clinical experts agreed it could be used as a second-line treatment. The company responded to the ERG's clarification questions on its submission, noting that tebentafusp was positioned as a first-line treatment. It explained that if tebentafusp were recommended by NICE, only people already having treatment for advanced uveal melanoma would be likely to have it at second line. The committee accepted that some people may have tebentafusp as a second-line treatment, although the numbers would decrease over time if tebentafusp was used as a first-line treatment. The committee concluded that tebentafusp would be used primarily as a first-line treatment for advanced uveal melanoma, in line with the IMCgp100-202 trial.

Generalisability of the clinical evidence

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

3.5 IMCgp100-202 assessed the clinical effectiveness of tebentafusp compared with investigator's choice (either pembrolizumab, ipilimumab or dacarbazine) in HLA-A*02:01-positive advanced uveal melanoma. Pembrolizumab was the most used treatment in the comparator arm (82%), then ipilimumab (13%), then dacarbazine (6%). The ERG highlighted that not all the comparators in the NICE

scope had been included in the investigator's choice arm. The clinical expert, who was also the principal investigator in the trial, noted that the comparator in the trial being investigator's choice reflected the lack of standard care for uveal melanoma (see section 3.2). After consultation, the company updated its analyses to compare tebentafusp with pembrolizumab (see section 3.6). To inform this comparison it used the subgroup of people in the trial who were preselected before randomisation to have pembrolizumab. The ERG felt this approach would reduce potential selection bias caused by any imbalance in prognostic factors (from the investigator's choice out of the 3 comparators). The committee accepted this approach. The mean age of people in the IMCgp100-202 trial was 62 years. The patient experts explained that some people are diagnosed with uveal melanoma in their 30s. The clinical experts explained that they would expect the median age of the population having treatment in practice to be around 62 years or younger. They noted that tebentafusp is not suitable for some older people who might not be fit enough to have treatment. The committee also noted that it would only be suitable for people with HLA-A*02:01-positive melanoma (around 50% of the uveal melanoma population) as specified in the trial (see section 3.4). The committee concluded that the investigator's choice arm reflected the treatments usually used for advanced uveal melanoma, and the population of the trial was generalisable to NHS practice.

The clinical-effectiveness results for the 82% of people who had pembrolizumab in the trial are the most relevant to NHS clinical practice

3.6 The comparators in the scope for first-line treatment of advanced uveal melanoma were pembrolizumab, ipilimumab, nivolumab alone or with ipilimumab, and dacarbazine. For previously treated disease the comparator in the scope was best supportive care. The committee agreed that tebentafusp would be used primarily as a first-line treatment (see section 3.4) so the appropriate comparator should be an active treatment. The ERG stated that all the comparators included in the scope should be included in the model. The clinical experts noted that pembrolizumab is the most frequently used treatment for advanced uveal melanoma (see section 3.2). The committee noted that in the investigator's choice arm of IMCgp100-202 a large proportion of people were taking

pembrolizumab. It agreed that this population drives the outcomes for this arm. Subgroup data suggested worse outcomes with dacarbazine, and better outcomes for ipilimumab compared with pembrolizumab. But the data for dacarbazine and ipilimumab came from a very small number of people so was highly uncertain. The committee acknowledged that other treatments are sometimes used for treating advanced uveal melanoma, but agreed that pembrolizumab was the most relevant comparator. It concluded that data from the large subgroup of people who had pembrolizumab, making up 82% of the investigator's choice arm in the trial, was suitable to assess the comparative clinical effectiveness of tebentafusp. After consultation, the company updated its cost-effective modelling to be based on a comparison of people:

- preselected to have pembrolizumab who were randomised to tebentafusp
- preselected to have pembrolizumab who were randomised to pembrolizumab.

The committee accepted this approach.

Clinical evidence results

Overall-survival data from the IMCgp100-202 trial suggests tebentafusp improves overall survival compared with usual treatments

3.7 At the October 2020 data cut, the median overall survival was longer in the tebentafusp arm (21.7 months) than in the investigator's choice arm (16.0 months). The difference in median overall survival was 5.7 months (hazard ratio [HR] 0.51, 95% confidence interval [CI] 0.37 to 0.71). Trial results for the 3-year follow-up analysis (June 2023 data cut) also showed the median overall survival was longer in the tebentafusp arm (21.6 months; 95% CI 19.0 to 24.3) compared with the investigator's choice arm (16.9 months; 95% CI 12.9 to 19.5; HR 0.68 95%, CI 0.54 to 0.87). Overall-survival data for the subgroup in the trial who were preselected to have pembrolizumab (n=199) before randomisation (see section 3.5) was presented at the second committee meeting (November 2022 data cut). These results are academic in confidence so cannot be reported here.

The committee agreed that the overall-survival data was now mature and concluded that tebentafusp likely improves overall survival compared with usual treatments.

Tebentafusp seems to have a benefit after disease progression but the reason for this is unclear

3.8 At the October 2020 data cut, median progression-free survival was longer in the tebentafusp arm than in the investigator's choice arm. But the extent of tebentafusp's benefit on progression-free survival appeared to be lower than on overall survival. Median progression-free survival was 3.3 months in the tebentafusp arm and 2.9 months in the investigator's choice arm. The difference in median progression-free survival was 0.4 months (HR 0.73, 95% CI 0.58 to 0.94). The committee noted the difference in the benefit shown for overall survival and progression-free survival. The clinical experts explained that disease progression was measured with the RECIST criteria (a radiographic measure of disease progression) in the trial. But they explained that the benefits of tebentafusp may not stop after disease progression as shown in the trial, possibly because of changes in the tumour microenvironment caused by tebentafusp. The committee concluded that although the evidence shows progression-free survival benefit with tebentafusp is limited, tebentafusp likely improves overall survival for people with advanced uveal melanoma. The committee further concluded that there seems to be a benefit with tebentafusp after disease progression according to RECIST criteria, but the reasons for this are unclear.

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

3.9 In IMCgp100-202 the number of people having any grade 3 or above treatment-emergent adverse event was higher in the tebentafusp arm than in the investigator's choice arm. This data is academic in confidence so cannot be reported here. The most common adverse event reported in the tebentafusp arm was cytokine release syndrome of any grade, which was determined retrospectively. The marketing authorisation for tebentafusp states that people

should be monitored overnight for cytokine release syndrome after each of the first 3 doses. Other adverse events reported more often by people in the tebentafusp arm included rash, pyrexia (fever), pruritus (itchy skin) and fatigue. The clinical experts explained that although there can be adverse events associated with tebentafusp, these are usually limited to the first 4 weeks of treatment. They explained that if tebentafusp is tolerated beyond this point, toxicity throughout the rest of treatment is very low and quality of life is often improved compared with before starting treatment. The patient experts agreed that the adverse-event profile of tebentafusp was better compared with other usual treatment options and that the adverse events that did occur were tolerable. They explained that while having tebentafusp, many people could continue life as they had done before treatment. The committee concluded that although the trial evidence suggests that there are more adverse events associated with tebentafusp than with the usual treatments, these are likely to happen within the first month. After this tebentafusp is well tolerated.

The economic model

The company's model structure is acceptable for decision making

3.10 The company presented a 3-state partitioned survival model to estimate the cost effectiveness of tebentafusp compared with the usual treatments. The 3 health states were progression-free, progressed-disease and death. The starting age in the model was 62 years, in line with the mean age in the clinical trial (see section 3.5). A time horizon of 38 years, equating to a lifetime, was used. The committee concluded that the partitioned survival model presented by the company was acceptable for decision making.

Survival modelling

Overall-survival modelling is highly uncertain

3.11 The company modelled overall survival based on extrapolation of data from

IMCgp100-202. Before consultation, the company selected a 3-knot spline model because a change in survival profile could not be captured by a standard parametric model. The ERG preferred standard parametric models applied to both arms to extrapolate overall survival from the trial data. At the first meeting the clinical experts explained tebentafusp has a novel mechanism of action. So, it is reasonable to assume that post-progression survival is different after tebentafusp than after immunotherapy, so using a different modelling approach in each arm may be reasonable. The clinical experts also suggested that uveal melanoma is an aggressive disease and that there is no expectation that tebentafusp would be curative. After consultation, the company updated its modelling approach for overall survival based on the April 2022 data cut of IMCgp100-202. It compared the tebentafusp subgroup preselected to have pembrolizumab with the pembrolizumab subgroup of the investigator's choice arm in IMCgp100-202, using a piecewise model for the tebentafusp arm (in which separate survival models are fitted to defined portions of survival data). The company noted that in the pembrolizumab subgroup, the hazard ratios continued to increase, suggesting that the longer the survival the higher the risk of death. This supported its choice to maintain a Weibull extrapolation. The hazard plot in the tebentafusp group had 2 phases. The hazard increased in the first phase and decreased in the second. So, the company used a piecewise model to fit separate survival models to defined portions of the observed survival data. Kaplan–Meier data from the trial showed that the survival probability rapidly decreased with time, followed by a phase where survival probability decreased more slowly. The committee felt there was still uncertainty in the overall-survival modelling. It accepted that the Kaplan–Meier and hazard plots showed the hazards increasing and decreasing. But it noted the decrease in hazards was only based on a limited number of people. So, it was less certain of the factors that were driving this. The committee agreed that standard parametric modelling would be the starting point for modelling survival. A subset of parametric models can adequately capture an increase and then a decrease in hazards.

Appeal outcome

3.12 Following publication of guidance in which tebentafusp was not recommended, the company and other stakeholders submitted an appeal. The appeal panel upheld the appeal points on matters relating to the committee's preferences on

the survival modelling and best-supportive-care costs. The appeal panel concluded that additional expert clinical input would be particularly important to inform the committee's judgements on areas of important remaining uncertainty. This included:

- the most appropriate choice, and interpretation of survival curve models to interrogate the available data (see section 3.11) and
- the most appropriate means of allocating supportive care costs in the model (see sections 3.18 and 3.19).

In response to the upheld appeal points, NICE commissioned its DSU to present a report. The DSU used a structured approach to elicit expert estimates of the expected survival of people with uveal melanoma having pembrolizumab and those having tebentafusp, and the uncertainty around these estimates. It also elicited expert opinion on the resources used in the provision of best supportive care for people with uveal melanoma over the course of their disease after progression. The company was given the opportunity to update its economic analysis in the light of the findings of the DSU report and the committee considered this new evidence at the third committee meeting.

Expert elicitation of long-term overall survival

3.13 The committee considered the results of the DSU structured expert elicitation approach. The approach used the Sheffield Elicitation Framework (SHELF) protocol. Clinical expert judgements were gathered on the proportion of people who would still be alive at 8 years after randomisation in the IMCgp100-202 trial in either the tebentafusp or pembrolizumab arm. The clinical experts met in either face-to-face or online workshops to consider evidence relating to the main trial and wider use of tebentafusp. All experts felt tebentafusp was more effective than pembrolizumab. The results from the online group (n=6) reported a median 8-year survival probability of 0.10 (95% credible interval 0.04 to 0.18) for the tebentafusp arm and 0.07 (95% credible interval 0.02 to 0.17) for the pembrolizumab arm. The face-to-face group (n=5) reported a median 8-year overall-survival probability of 0.13 (95% credible interval 0.05 to 0.19) for the tebentafusp arm and 0.09 (95% credible interval 0.04 to 0.17) for the

pembrolizumab arm. At the third meeting, the company raised several concerns with the DSU methodology. Its concerns were:

- The most experienced clinical experts had not been included in the DSU elicitation workshops. It also noted that in clinical practice there are only a small number of healthcare professionals with extensive experience treating uveal melanoma with tebentafusp in the NHS. The DSU explained it had followed a rigorous expert selection process, which included experts identified by the company. But clinical experts who had attended the previous committee meetings or advisory board meetings for this topic were excluded. This was to avoid anchoring bias, in people who may have previously seen the extrapolation models, and potentially influencing opinions. The clinical and patient experts at the third committee meeting also supported the company's concerns that clinical experience in the workshops had been under-represented. They noted that most people currently have tebentafusp at 3 clinical centres in the UK. But the elicitation exercise had excluded clinical experts in 2 of these centres. So, their view was that the predicted overall-survival outcomes resulting from the workshops would be highly uncertain.
- The choice of an 8-year overall-survival estimate was arbitrary. The DSU explained that this option was chosen because it was not too close to the tail on the Kaplan–Meier curve (which would not have been useful in predicting model choices) but was not too far in the future to express opinion. Clinical experts in the workshops agreed that there was no additional challenge in using an 8-year time point for the elicitation exercises compared with 5- and 10-year landmark time points more commonly used in survival analysis.
- At the third committee meeting the clinical experts noted that the 8-year survival estimate produced by the DSU for the pembrolizumab arm lacked face validity. In clinical practice, it would be very rare for a person with advanced or metastatic uveal melanoma who had had pembrolizumab to live beyond 8 years.
- The company also explained that the estimates in the DSU elicitation report differed from the published primary analysis for IMCgp100-202 (see section 3.7) and the 3-year analysis (median overall survival of 21.6 months in the tebentafusp arm compared with 16.9 months in the investigator's choice arm [HR 0.68; 95% CI 0.54 to 0.87]).

- The company argued that the data reported by Rantala et al. (2019) was the most clinically robust evidence to compare first-line tebentafusp with pembrolizumab. The ERG noted that the Rantala et al. data was a lower benchmark. This was because only a small number of people in the dataset had pembrolizumab and the majority included in the study had it as a second-line treatment. The committee noted this uncertainty.
- The clinical experts taking part in the elicitation workshops noted that a subgroup of people with uveal melanoma with specific mutations may have longer survival. But, the company felt this might confound participant predictions. In addition, the company highlighted that using tebentafusp as a subsequent treatment to pembrolizumab can confound the overall-survival predictions in the pembrolizumab group.

  At the third meeting the committee acknowledged the concerns of the company and experts about the limitations in the expert elicitation exercise. It concluded that the results of the DSU exercise, while uncertain, would be helpful in informing decisions on how to extrapolate overall-survival data in the modelling.

Company post-appeal overall-survival modelling

3.14 Following the appeal and in the light of the DSU expert elicitation, the company updated its overall-survival modelling approach. It retained a piecewise approach to extrapolate overall survival with tebentafusp, altering the cut to 26 months and applying a log-logistic distribution. The company felt a standard parametric distribution would not capture the long-term survivors who might have long-term benefits with tebentafusp. This gave an 8-year overall-survival probability of 16.2%, which was within the 95% credible interval range (6% to 18%) in the DSU elicitation results. It retained a standard parametric approach for pembrolizumab (amending to a log-normal distribution, which was best fitting based on visual model inspection). This gave an 8-year overall-survival probability of 5.6%. The company viewed this as a conservative estimate. The ERG found the log-normal distribution to be plausible. But, it noted that overall-survival extrapolation remained uncertain. So, it presented 3 additional scenarios:

- log-logistic distribution for both treatments
- log-normal distribution for both treatments, and
- log-logistic distribution for tebentafusp, and generalised gamma distribution for pembrolizumab.

The committee noted the resulting overall-survival estimates for these scenarios were also within the range identified in the DSU workshops. But this data is commercial in confidence so cannot be reported here. The committee recalled it had been uncertain about the earlier estimates of long-term overall survival for tebentafusp (see section 3.11) and it had preferred a standard parametric approach. It noted that the company's updated overall-survival modelling for both tebentafusp and pembrolizumab gave 8-year overall-survival probabilities that lay within the range of estimates elicited in the DSU workshops. The committee concluded that the company's updated overall-survival modelling, and that done by the ERG, were within the range of estimates provided by the DSU expert elicitation exercise and therefore plausible. But both the company and ERG modelling were extremely uncertain.

Either piecewise or fully parametric models are reasonable for estimating progression-free survival and time on treatment

3.15 The company used a piecewise modelling approach to estimate progression-free survival and time on treatment in both arms. For progression-free survival it used Kaplan–Meier data and an extrapolated generalised gamma tail at the point where 15% of the population remained at risk. For time on treatment, it used Kaplan–Meier data with an exponential model tail from the point where 15% of the population remained at risk in the investigator's choice arm. For the tebentafusp arm, an exponential model tail was used from the point where 25% remained at risk. The ERG suggested that the Kaplan–Meier data may overfit the trial data and that the cut-points chosen by the company for extrapolation were arbitrary. It preferred to use a fully parametric generalised gamma extrapolation for both arms to estimate both outcomes. The clinical experts explained that time on treatment reflected time to progression because tebentafusp was stopped in the

trial when progression was confirmed. They noted that the mean tebentafusp treatment duration in the trial was in line with the estimated progression-free survival in the company's model. After consultation, the company updated the data for time on treatment in the economic model using the April 2022 dataset from the trial. The committee discussed whether a piecewise approach was the most appropriate extrapolation to model progression-free survival. The company retained its piecewise modelling approach. The data showed a rapid decrease in progression-free survival, followed by a flattening of the data. The company used Kaplan–Meier data to model the rapid decrease. It felt that the generalised gamma function best represented the extrapolation where the data flattened. The data suggested that tebentafusp had a smaller effect on progression-free survival than on overall-survival estimates. The clinical expert explained that, because of its mode of action, progression-free survival is not the most sensitive way to measure the effects of tebentafusp. Given that the progression-free survival data in the trial is mature, the impact on the cost-effectiveness results of using different methods of extrapolation was minimal. The committee concluded that the company and the ERG had different approaches to estimating progression-free survival and time on treatment. But it agreed that the differences had little impact on the cost-effectiveness results.

Assumptions in the economic model

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

3.16 The company included a 2-year stopping rule in its model. It stated that it did not expect people to take tebentafusp for longer than 2 years in practice so it did not include the costs for treatment beyond this time. It highlighted that its model predicted that less than 5% of people were still having tebentafusp after 2 years so it was reasonable to include the stopping rule at this point. There was no 2-year stopping rule in the trial, and treatment was only stopped after disease progression according to RECIST criteria. So, any benefits associated with tebentafusp beyond 2 years are included in the clinical-effectiveness results and the model. The patient experts suggested that tebentafusp is well tolerated so there is no logical reason to stop treatment while it is still effective. They

explained that it was unlikely to be acceptable to people to stop having tebentafusp without evidence of a sustained benefit after stopping. The clinical experts explained that there is no clinical data on whether a treatment effect would continue after stopping treatment at 2 years, or to show the impact on survival outcomes. But it is plausible that the treatment effect would not wane instantly after stopping treatment. This is because in the trial there was a benefit in overall survival beyond the point of stopping treatment. The committee concluded that it was not appropriate to include a stopping rule in the model because the clinical rationale for it had not been adequately justified. After consultation, the company updated its base case to remove the 2-year stopping rule.

The choice of approach for estimating utility values is unlikely to be a driver of the cost-effectiveness results

3.17 Based on Hatswell et al. (2014), the company noted that quality of life for people with advanced melanoma may be affected more by length of time to death than by disease progression. So, it used a time-to-death approach to calculate utility values in its model, which categorises utility based on the length of time before death. The company stated that the number of observations by time-to-death categories would have been insufficient for it to use the EQ-5D data from the trial. So, it used the utility values from NICE's technology appraisal guidance on pembrolizumab for advanced melanoma not previously treated with ipilimumab. It calculated the relative reduction for the different periods until death and applied these multipliers for each interval to utilities from the IMCgp100-202 trial. The ERG disputed the use of the time-to-death approach because it was inconsistent with the model structure. This is because the utilities did not differentiate between the progression-free and progressed health states. So, the health states did not reflect the decline in health-related quality of life after progression. Also, the ERG noted that the company applied an age-adjustment factor to apply a decrease in utility based on values for the UK population. Despite this, in the company's base case, the utility value for people over 62 years having treatment was higher than the average utility value for the UK population. It stated that EQ-5D data was available from the trial, which was more appropriate to use than data from a different type of melanoma. The company suggested that it was more appropriate to use published utilities because of missing data in the EQ-5D

data from IMCgp100-202. It used 3 imputation approaches to account for the missing data (mean imputation at baseline, multiple imputation in the treatment phase and data missing completely at random in the follow-up period). But the ERG felt that these imputation approaches could introduce bias because:

- mean imputation could underestimate the variance of the data, disturb relationships between variables, and affect the mean estimate if data is missing for reasons other than completely at random
- missing data increased as trial follow up increased, which suggested the data was unlikely to be missing completely at random
- the company removed incomplete data before analyses for the survival follow-up period, which could bias estimates.

The company suggested that the time-to-death approach was more appropriate than utilities from on- and off-treatment health states. This is because disease progression is not a good marker of quality of life in people who have had tebentafusp. The clinical and patient experts agreed that reasonably good quality of life could be maintained after progression according to RECIST criteria. They noted that deterioration in quality of life happens quickly towards the end of life for many people with advanced uveal melanoma. The committee noted that the time-to-death and on- and off-treatment health-state utility approaches were both uncertain. It noted that the company and ERG both used the time-to-death approach in their base-case analyses. It concluded that the time-to-death approach is not consistent with a model structure designed to reflect health-state utilities. But the choice of approach to estimate utility values was unlikely to be an important driver of the cost-effectiveness results.

The estimated costs of subsequent treatment are uncertain

3.18 Many people in IMCgp100-202 went on to have another treatment after they had stopped having the active treatment. In its model, the company used dacarbazine to represent chemotherapy, and pembrolizumab, ipilimumab, nivolumab, and ipilimumab plus nivolumab to represent immunotherapies. The data for subsequent treatments was taken from those used in the IMCgp100-202 trial. But

the NHS England representative said that some of these treatments did not reflect those that would be used in practice. The company applied subsequent costs as a one-off cost when treatment stopped and reflected the costs of best supportive care for an average of 4 months. It based this assumption on a study by McKendrick et al. (2016). But the ERG noted that the 4-month duration was not related to the estimated time people might be in the progressed-disease health state. The ERG found that applying costs of best supportive care per cycle while people were in the progressed-disease health state was most appropriate. The committee agreed that applying costs for people in the pembrolizumab arm who had subsequent pembrolizumab might inappropriately inflate the costs in that arm. The clinical experts explained that in practice treatment would usually stop if the disease had progressed, so costs would not accrue in that time. In the company model there were one-off costs attributed at the time of disease progression to reflect best supportive care and end-of-life care. Given the clinical expert's comments, the committee agreed that only one of these costs was needed. This meant there was some uncertainty in the estimates of applying the costs for subsequent treatment. But it decided this had a limited impact on the cost-effectiveness results.

3.19 At the third committee meeting, the committee discussed the results of a DSU online survey of expert opinion on resource use for best supportive care in uveal melanoma after disease progression. The DSU survey results recognised that people with symptoms of disease progression would need supportive care, such as palliative care and further monitoring. But people who were asymptomatic would only need resources associated with disease monitoring. One clinical expert involved in the DSU exercise had suggested that the median life expectancy might be 9 to 12 months after disease progression. But at the third committee meeting, one of the clinical experts present suggested the median life expectancy is around 3 to 6 months. The vast majority of people have supportive care in the last few months of life. The patient representatives who had experience of advanced disease agreed and said that disease progression could happen quickly and over a short period of time. The committee recognised that the best-supportive-care costs would vary based on presence of symptoms. But it concluded it was likely the company's one-off modelling would be representative of how supportive care costs are applied in NHS clinical practice.

Treatment adherence in the pembrolizumab arm should be

consistent with the tebentafusp arm

3.20 In its original base case, the company assumed a 95% adherence in the tebentafusp arm. After consultation it amended this to 92%. Adherence affected drug and administration costs. But the company did not apply an adherence correction for pembrolizumab. The ERG felt it was unlikely that adherence would be 100% in either arm. Its original exploratory analyses had assumed the same adherence in both arms. But because of limitations in the company's model provided after consultation, the ERG was not able to explore the impact of this assumption in its updated analyses. The ERG preferred to either include an adherence correction for pembrolizumab, to maintain consistency with the tebentafusp arm, or to not apply any adherence correction in either the tebentafusp or pembrolizumab arm. The committee noted these differences between the company and ERG models. It concluded that adherence would not be 100% for both treatments and, in the absence of evidence of a difference between treatments, a consistent adjustment in both arms should be applied.

The cost of HLA-A*02:01 testing is appropriately included in the model.

3.21 The marketing authorisation for tebentafusp only includes people with HLA-A*02:01-positive uveal melanoma (see section 2.1). The clinical experts noted that people with uveal melanoma are not tested for HLA-A*02:01 in current practice. So, if tebentafusp was a treatment option, all people with advanced uveal melanoma would need to have testing. They explained that HLA-A*02:01 testing is routinely done for other conditions and would be easily implementable in this setting. The company included the costs of HLA-A*02:01 testing in its model. The committee agreed that it was appropriate to include the costs of testing in the model and that this would be simple to adopt in practice.

End of life

Tebentafusp meets the end-of-life criteria for advanced uveal melanoma

3.22 The committee discussed the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal 2013. Data from the October 2020 data cut of IMCgp100-202 showed that for people in the investigator's choice arm, median overall survival was 16.0 months (see section 3.7). IMCgp100-202 showed an increase in median overall survival with tebentafusp of 5.7 months. The clinical experts agreed that usually time from diagnosis to death with immunotherapy treatment was less than 2 years and that tebentafusp was expected to improve life expectancy by at least 3 months on average. The committee concluded that based on the clinical trial evidence tebentafusp meets the end-of-life criteria for treating advanced uveal melanoma.

Acceptable incremental cost-effectiveness ratio

3.23 The committee recalled that it had previously indicated a threshold of £50,000 per quality-adjusted life-year (QALY) gained would be appropriate, when evaluating the cost effectiveness using the ERG assumptions. This included a threshold at the upper end of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained) and applying the end-of-life criteria weighting (see section 3.22), which multiplies this threshold by 1.7. At the third committee meeting it reconsidered this threshold noting that NICE's guide to the methods of technology appraisal 2013 states that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. It recalled that the company's modelling for both tebentafusp and pembrolizumab gave overall-survival probabilities within the DSU expert elicitation range (see section 3.14). But it noted that the ERG's estimated survival estimates were also within the range of estimates provided by

the DSU expert elicitation exercise, but the resulting ICERs were considerably higher than the company's estimates. This underlined the very high level of uncertainty associated with predicting the long-term overall-survival benefit for tebentafusp. The committee concluded that if it were to accept the company's survival extrapolations, then the maximum acceptable ICER would be at the lower end of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained) to account for this uncertainty. When applying the end-of-life criteria an acceptable ICER would be around £39,000 per QALY gained.

Cost effectiveness

The cost-effectiveness estimates are within the range NICE considers a cost-effective use of NHS resources

3.24 The committee discussed its preferred assumptions:

- After considering the results of the expert elicitation exercise, it noted that the company's modelling gave overall-survival probabilities within the DSU expert elicitation range (see section 3.14), and so the survival estimates could be applied with associated high uncertainty. Applying best-supportive-care costs after disease progression as a one-off cost (as in the company's base case) is likely to be most representative of how the costs are applied in NHS clinical practice (see sections 3.18 and 3.19).
- It decided that a 2-year stopping rule would not apply (see section 3.16).

The committee noted that other assumptions that differed between the company and ERG models had a limited impact on the cost-effectiveness results. These included:

- using piecewise (as in the company's base case) or fully parametric (as in the ERG's exploratory base case) for progression-free survival and time-on-treatment extrapolation methods (see section 3.15)
- assuming 92% adherence in the tebentafusp arm (as in the company's base

case) or assuming the same adherence in both arms (as in the ERG's exploratory base case; see section 3.20).

Tebentafusp has a patient access scheme. Because of confidential commercial arrangements for comparator treatments, the ICERs are confidential and cannot be reported here. Based on the committee's preferred assumptions, the ICER was within the range the committee had agreed would be a cost-effective use of NHS resources (see section 3.23). The committee concluded that tebentafusp is recommended for routine use in the NHS.

Innovation

Tebentafusp is an innovative new treatment

3.25 The clinical experts explained that tebentafusp is a new drug with a novel mechanism of action (see section 3.3). They explained that there is no standard care for advanced uveal melanoma (see section 3.2) and that tebentafusp would be the first treatment to target the specific features of the disease. The patient experts explained that tebentafusp would be a step change in the treatment of advanced uveal melanoma. The committee concluded that tebentafusp is innovative. But it agreed that all the health-related quality-of-life gains had been captured in the QALY calculations.

Equality issues

3.26 At consultation, one consultee said that ocular melanoma is usually seen in older people but that many people who are still working age will continue to work through the diagnosis. The committee noted that the technology is evaluated in line with its marketing authorisation, which does not restrict use of tebentafusp to people of different ages. It did not consider this as an equality issue. It did not identify any other equality issues.

Conclusion

Tebentafusp is recommended

3.27 The committee noted that tebentafusp is cost effective, when considering the end-of-life criteria (see section 3.24). So, tebentafusp is recommended for use in the NHS for treating advanced uveal melanoma.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has advanced uveal melanoma and the healthcare professional responsible for their care thinks that tebentafusp is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

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

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

Chair

James Fotheringham
Vice chair, technology appraisal committee A

NICE project team

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

Albany Meikle and Victoria Gillis-Elliott
Technical leads

Mary Hughes, Christian Griffiths and Victoria Kelly
Technical advisers

Thomas Feist and Jennifer Upton
Project managers

Janet Robertson
Associate director

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