NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Tebentafusp for treating advanced uveal melanoma

1 Recommendations

1.1 Tebentafusp is not recommended, within its marketing authorisation, for treating HLA-A*02:01-positive unresectable or metastatic uveal melanoma in adults.

1.2 This recommendation is not intended to affect treatment with tebentafusp that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

There is no standard treatment 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 the length of time before their cancer gets worse compared with the usual treatments offered.

Tebentafusp meets the criteria for a life-extending treatment at the end of life and is likely to increase how long people live. But the most likely cost-effectiveness

estimates are uncertain and higher than what NICE considers an acceptable use of NHS resources for end of life treatments. So, tebentafusp is not 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 microgram per 1 ml vial) is £10,114 (BNF online accessed July 2023).

The company has a commercial arrangement, which would have applied if the technology had been recommended.

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. See the committee papers for full details of the evidence.

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 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 treating advanced uveal melanoma

3.2 The patient and clinical experts explained that there is no standard care for treating 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 take 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 treating 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 which 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 be targeted by tebentafusp, potentially also 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 considered 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 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 considered 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 considered 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 IMCgp100-202 is an ongoing trial. 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 0.51, 95% confidence interval [CI] 0.37 to 0.71). Trial results for the August 2021 and February 2022 data cuts, and data from the April 2022 data cut were presented at the second committee meeting but are academic in confidence so cannot be reported here. Overall survival data from the most recent data cut (November 2022) for the subgroup in the trial who were preselected to have pembrolizumab (n=199) before randomisation (see section 3.5) was also presented at the second committee meeting. These results are also academic in confidence so cannot be reported here. The committee noted that the overall survival data used in the model (from the August 2021 data cut) included some people who had crossed over from the investigator's choice arm to have tebentafusp, but the results had not been adjusted. This contributed to some uncertainty in the results, so the committee would have preferred that the crossover had been adjusted for. But the company did not consider adjusting for crossover was feasible using standard methods because the trial protocol

did not mandate crossover. It considered that a statistical analysis to adjust for differences between those who did and did not cross over was not appropriate because too few people in the trial crossed over. The ERG clarified that the company's approach was methodologically the most robust approach, because it mirrored the crossover that would be seen in clinical practice. The committee accepted this. It considered 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 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 (hazard ratio 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 treatment started. 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 on 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, and 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 but standard parametric approaches are the most appropriate

3.11 The company modelled overall survival based on extrapolation of data from IMCgp100-202. Before consultation, it used a 3-knot spline model for extrapolation of overall survival in the tebentafusp arm and a Weibull model for extrapolation in the investigator's choice arm. The company noted that the choice to use a spline model was because of a change in survival profile which 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. The committee noted that the company's spline model for tebentafusp followed the observed trial Kaplan–Meier data closely at first, but at the end of the observed data it plateaued above the Kaplan–Meier curve. The ERG's preferred log-logistic or generalised gamma curves did not have a plateau for the period after the observed trial data and resulted in a much lower modelled mean overall survival for tebentafusp. 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 suggested that uveal melanoma is an aggressive disease and that there is no expectation that tebentafusp would be curative. So it is not expected that the overall survival curve would plateau, indicating disease cure, as suggested by the company's approach. The committee noted that most of the gains in overall survival made in the economic model are accumulated beyond the observed trial data. So the model is driven by the extrapolation of trial data, which is associated with uncertainty. Also, the

committee noted that the choice of overall survival extrapolation has a large impact on the modelled overall survival and the cost-effectiveness results. The committee considered that standard parametric curves should be the starting point for modelling and could be used for this treatment. After consultation, the company updated its modelling approach for overall survival:

- using different parametric models for the tebentafusp and investigator's choice arms
- updating its data analyses based upon the April 2022 data cut of the IMCgp100-202 trial
- comparing the tebentafusp subgroup preselected to have pembrolizumab with the pembrolizumab subgroup of the investigator's choice arm in the IMCgp100-202 trial
- using a piecewise model for the tebentafusp arm (in which separate survival models are fitted to defined portions of survival data).

The company chose different approaches to model the tebentafusp and investigator's choice groups in its economic model. It 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. In the first phase, the hazard increased, and in the second phase, decreased. 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 considered there was still uncertainty in the overall survival modelling:

- The company used visual inspection of the hazards plot, to identify the appropriate cut-off point to fit a different model. It used the Kaplan–Meier data where the hazard increased and a standard parametric model where the hazard decreased.

- The committee 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 limited number of people. So it was less certain of the factors that were driving this.
- Other fully parametric survival models might also produce similar modelled effects.

The committee concluded that the overall survival modelling was highly uncertain, but the company's approach appeared to overestimate the proportion of people surviving in the long term. This is because it generated extrapolations suggesting that people did not appear to die in the period modelled by the parametric section. On balance, using a standard parametric approach to extrapolate the data in both treatment arms was preferred.

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

3.12 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, and from where 25% remained at risk in the tebentafusp arm. 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 considered 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 considered 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 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

3.13 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: treatment was only stopped after disease progression according to RECIST criteria. So any benefits associated with tebentafusp treatment 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 patients to stop treatment 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, 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

3.14 Based on a study by Hatswell et al. 2014, the company noted that the quality of life of people with advanced melanoma may be affected more by the length of time to death than by disease progression status. 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 of 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 considered 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

3.15 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 stated 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 a progressive disease health state. The ERG considered that applying costs of best supportive care per cycle while people were in a progressive disease health state was most appropriate. The committee considered that applying costs for people in the pembrolizumab arm who had subsequent pembrolizumab might inappropriately inflate the costs in the pembrolizumab 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 to reflect end of life. Given the clinical expert's comments, it considered that only one of these costs was needed. This means there was some uncertainty in the estimates of applying the costs for subsequent treatment. But it considered this had a limited impact on the cost-effectiveness results.

Treatment adherence in the pembrolizumab arm should be consistent with that in the tebentafusp arm

3.16 In its original base case, the company assumed a 95% adherence in the tebentafusp arm. After consultation it amended this to be 92%. Adherence affected drug and administration costs. But the company did not apply an

adherence correction for pembrolizumab. The ERG considered 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 arms. The committee noted these differences between the company and ERG models, but considered that that treatment adherence would not be at 100% for pembrolizumab and some adjustment should be applied.

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

3.17 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 and that if tebentafusp were 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

3.18 The committee considered 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.

Cost effectiveness

The cost-effectiveness estimates are higher than what NICE considers a cost-effective use of NHS resources

3.19 The committee discussed its preferred assumptions, which included using standard parametric curves for extrapolating overall survival (as in the ERG's base case; see section 3.11). It noted that other assumptions which 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) progression-free survival and time on treatment extrapolation methods (see section 3.11)
- applying best supportive care costs as one-off costs (as in the company's base case) or per cycle costs (as in the ERG's exploratory base case; 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 3.16).

Tebentafusp has a patient access scheme. Because of confidential commercial arrangements for comparator treatments, the incremental cost-effectiveness ratios (ICERs) are confidential and cannot be reported here. As the end of life criteria were met (see section 3.18), the committee considered that for tebentafusp to be an effective use of NHS resources, the ICER should not be above £50,000 per quality-adjusted life year (QALY) gained. Based on the company's preferred assumptions, the

ICER was above £50,000, and the ERG's exploratory base case ICERs (using either a generalised gamma or log-logistic overall survival extrapolation) were both above £250,000 per QALY gained. The committee was aware that the biggest driver of the difference between the company's and the ERG's ICERs was the choice of overall survival extrapolation (see section 3.11). Using either a generalised gamma or log-logistic overall survival extrapolation increased the ERG's base case ICERs substantially. The committee concluded that the ERG's ICERs did include its preferred assumptions of using a standard parametric modelling approach to estimate overall survival. So, the ERG's ICERs reflected the committee's preferred assumptions more than the company base case.

Innovation

Tebentafusp is an innovative new treatment

3.20 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 uveal melanoma. 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 considered that all the health-related quality of life gains had been captured in the QALY calculations.

Equality issues

3.21 At consultation, one consultee stated 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 was an equality issue. It did not identify any other equalities issues.

Conclusion

Tebentafusp is not recommended for routine use

3.22 The committee noted that both the company's and the ERG's base case ICERs indicate that tebentafusp is not cost effective, even when considering the end of life criteria (see sections 3.18 and 3.19). Because of the uncertainty about the modelling of overall survival, the ICERs were also highly uncertain . So tebentafusp is not recommended for use in the NHS for treating advanced uveal melanoma.

Tebentafusp is not recommended in the Cancer Drugs Fund

3.23 Having concluded that tebentafusp could not be recommended for routine use, the committee then considered if it could be recommended for treating advanced uveal melanoma within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum). At the first committee meeting it was noted that:

- the company had indicated it was interested in the treatment being considered for funding through the Cancer Drugs Fund
- overall survival data used in the economic model was highly uncertain
- IMCgp100-202 is still ongoing and direct trial data could help reduce uncertainties around overall survival
- the systemic anti-cancer therapy dataset could provide additional survival data
- the economic model is suitable for decision making.

But the committee also noted that the most plausible ICER was over £250,000 per QALY gained (see section 3.11), and that the company's ICER was over £50,000 per QALY gained. So it agreed that no ICERs had been presented which showed plausible potential for tebentafusp to be cost effective. The committee was aware that if tebentafusp were to be included in the Cancer Drugs Fund, the NICE review of tebentafusp at the

end of the data collection arrangement would be done following NICE's recently updated health technology evaluations process and methods manual. Using these methods, the end of life criteria would not apply and it is unknown if the severity modifier would be applicable. Based on the ICERs presented, the committee concluded that tebentafusp did not meet the criteria to be considered for inclusion in the Cancer Drugs Fund.

4 Appraisal committee members and NICE project team

Appraisal committee members

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

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

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

Chair

Radha Todd

Chair, technology appraisal committee A

NICE project team

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

Albany Meikle and Victoria Gillis-Elliott

Technical lead

Mary Hughes and Christian Griffiths

Technical adviser

Thomas Feist

Project manager

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