NICE National Institute for Health and Care Excellence

NICE guidance

Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy

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 are 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 Recommendations

1.1 Pembrolizumab is recommended for use within the Cancer Drugs Fund as an option for treating locally advanced or metastatic urothelial carcinoma in adults who have had platinum-containing chemotherapy, only if:

- pembrolizumab is stopped at 2 years of uninterrupted treatment or earlier in the event of disease progression and
- the conditions in the managed access agreement for pembrolizumab are followed.

1.2 This recommendation is not intended to affect treatment with pembrolizumab 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

Treatment for previously treated locally advanced or metastatic urothelial carcinoma is docetaxel or paclitaxel. Clinical trial evidence shows that pembrolizumab significantly improves overall survival compared with these drugs.

Pembrolizumab meets NICE's criteria to be considered a life-extending treatment at the end of life. The most plausible cost-effectiveness estimate is uncertain because it is not clear which overall survival extrapolation is most appropriate to use for the economic modelling. Based on the company's commercial offer as part of the managed access agreement proposal, and the preferred assumptions and extrapolations, the cost-effectiveness estimates using either the evidence review group's or company's preferred overall survival extrapolation are between £44,504 and £46,447 per quality-adjusted life year (QALY) gained. This is in line with what NICE normally considers acceptable for end-of-life treatments (less than £50,000 per QALY gained), although other plausible estimates are higher. However, the cost-effectiveness estimates assume that, despite a 2-year stopping rule, the effect of pembrolizumab continues for the duration of the model (a lifetime continued treatment effect) which is implausible. Accounting for this effect increases cost-effectiveness estimates, although it's not certain by how much; some plausible estimates are more than £50,000 per QALY gained.

Pembrolizumab has plausible potential to be cost effective. Further data collection would reduce the uncertainty around overall survival and continued treatment effect. Therefore pembrolizumab can be recommended for use in the Cancer Drugs Fund.

Pembrolizumab appears to be more effective for people with urothelial carcinoma expressing the PD-L1 protein than for people who do not express PD-L1. However, the cost-effectiveness results for this group are not reliable so no recommendations can be made.

2 Information about pembrolizumab

Marketing authorisation indication	Pembrolizumab (Keytruda, Merck Sharp & Dohme) has a marketing authorisation for 'the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy'.
Dosage in the marketing authorisation	200 mg by intravenous infusion every 3 weeks until disease progression or unacceptable toxicity.
Price	£2,630 per 100 mg vial (excluding VAT; company submission). As part of the managed access agreement, the company has a commercial access agreement with NHS England. This makes pembrolizumab available at a reduced cost. The financial terms of the agreement are commercial in confidence.

3 Committee discussion

The appraisal committee (section 6) considered evidence submitted by Merck Sharp & Dohme and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

The condition

Locally advanced or metastatic urothelial carcinoma substantially decreases quality of life

3.1 Urothelial carcinoma causes a number of symptoms, including haematuria (blood in the urine) and increased frequency, urgency and pain associated with urination. Surgical treatments such as urostomy can have a substantial impact on quality of life and restrict daily activities. The patient experts explained that chemotherapy is associated with unpleasant side effects such as fatigue, nausea and vomiting and puts people at a greater risk of infection. The committee was aware that many people with locally advanced or metastatic urothelial carcinoma are older and may have comorbidities, which can affect treatment decisions. It recognised that locally advanced or metastatic urothelial carcinoma has a significant impact on quality of life.

Current treatments

There is unmet need for effective treatment options

3.2 Initial treatment for locally advanced or metastatic disease is usually with a cisplatin-containing chemotherapy regimen. However, cisplatin can be damaging to the kidneys, so is not suitable for some people with impaired kidney function or a poor performance status. People who have not had previous chemotherapy and for whom cisplatin is unsuitable will usually be offered carboplatin plus gemcitabine. If they are not well enough to tolerate this or they choose not to have it, best supportive care will be offered. Treatment options for people with disease progression after platinum-containing chemotherapy include docetaxel, paclitaxel or best supportive care. The clinical experts explained that none of the current treatments offer lasting benefit and that prognosis is poor even for people having their first therapy. The patient experts

explained that the side effects of chemotherapy can have a major negative impact on quality of life and that regular hospital visits for treatment disrupt usual activities. The clinical experts noted that there have been no new treatments for locally advanced or metastatic urothelial carcinoma for a number of years and that, unlike for other cancers, there is no targeted or personalised treatment. The committee concluded that there is an unmet need for effective treatment options for people with locally advanced or metastatic urothelial carcinoma.

Population

The trial evidence, in people who have had chemotherapy, is suitable for decision-making

3.3 The marketing authorisation for pembrolizumab includes people for whom cisplatin is unsuitable and people who have had previous platinum-containing chemotherapy. The company proposed that this appraisal focuses on the population who have had platinum-containing chemotherapy, because this reflects the trial evidence currently available. The remainder of the population covered by the marketing authorisation (for whom cisplatin is unsuitable) will be addressed in a subsequent appraisal when the relevant clinical evidence is available. The committee concluded that this approach is appropriate for decision-making, and recognised that it would only be able to make a recommendation for the population for whom evidence has been presented.

Comparators

Paclitaxel, docetaxel and best supportive care are relevant comparators for people who have had platinum-containing chemotherapy

3.4 The company submitted clinical and cost-effectiveness analyses comparing pembrolizumab with paclitaxel or docetaxel. Although best supportive care and re-treatment with first-line chemotherapy were comparators in the NICE scope, the company did not submit analyses comparing pembrolizumab with these treatments. The company considered that best supportive care would not be appropriate for people well enough to be offered pembrolizumab, and that there were not enough data for a comparison with best supportive care. The

committee understood that because pembrolizumab is an immunotherapy with a different side effect profile to taxanes (such as paclitaxel and docetaxel), there may be some people for whom pembrolizumab is suitable who would otherwise choose best supportive care. The committee recognised that with the introduction of immunotherapy practice may change, but that currently best supportive care remains a treatment option for urothelial carcinoma and is therefore a relevant comparator. The company stated that there was no evidence for re-treatment with first-line chemotherapy. The committee heard from the Cancer Drugs Fund clinical lead and clinical experts that re-treatment with first-line chemotherapy was used before a standard second-line treatment option was available, and that now most clinicians would use a taxane. The committee concluded that docetaxel, paclitaxel, and best supportive care were appropriate comparators, but re-treatment with first-line chemotherapy was not.

Clinical trial evidence

The KEYNOTE-045 post-hoc subgroup results are generalisable to UK clinical practice and most appropriate for decision-making

3.5 The clinical effectiveness evidence for pembrolizumab came from the September 2016 data cut of KEYNOTE-045, an open-label, randomised controlled trial. In its response to consultation the company submitted an updated economic model which incorporated a later data cut, from January 2017, to inform the cost-effectiveness estimates. The trial included people with disease progression or recurrence of urothelial cancer after treatment with a platinum-containing regimen (cisplatin or carboplatin). The trial recruited:

- 270 people randomised to have pembrolizumab
- 272 people randomised to have the investigator's choice of paclitaxel, docetaxel, or vinflunine.

The company recognised that vinflunine is not used in clinical practice in the UK, and did a post-hoc subgroup analysis which removed the population who were assigned vinflunine as a treatment. The investigator's choice of chemotherapy was assigned before randomisation, and therefore the post-hoc subgroup analysis also removed people who were subsequently randomised to have pembrolizumab. The post-hoc subgroup analysis included:

- 188 people randomised to have pembrolizumab
- 182 people randomised to have the investigator's choice of paclitaxel or docetaxel.

The clinical experts and the ERG explained that KEYNOTE-045 was well designed and conducted. The ERG considered that the trial was at low risk of bias, with the exception of lack of blinding because of the open-label design of the trial. The company explained that blinding was inappropriate in this study because people were likely to recognise which arm they had been assigned to based on the safety profile and method of administration of pembrolizumab. The clinical experts considered the results of the trial to be robust. The committee concluded that the trial was of good quality and the results informative for decision-making. It was aware that using post-hoc subgroup analyses introduces the risk of bias, and that excluding the vinflunine data reduces the statistical power of the trial. But the committee concluded that the post-hoc subgroup best reflects clinical practice in the UK and is the most appropriate evidence on which to base its decision-making.

Accounting for subsequent immunotherapy in KEYNOTE-045 using the 2-stage method is appropriate for decision-making

3.6 On disease progression, people in the trial could have subsequent anti-PD-L1 or PD-1 treatment including atezolizumab, avelumab, durvalumab, nivolumab, and pembrolizumab. The company explored adjusting overall survival to account for these treatments using the rank preserving structural failure time method (RPSFT), the inverse probability of censoring weights method (IPCW), and a 2-stage method. The company preferred the 2-stage method because the assumptions required for it to be valid were met. The ERG agreed that the unadjusted overall survival results would be the least appropriate for decision-making. It noted that the RPSFT method would be the least appropriate method to account for treatment switching because it censors patients before switching, and generates artificial survival times and assumes a common treatment effect for those who switch; people in KEYNOTE-045 were able to switch to a range of anti-PD-L1 or PD-1 treatments. The ERG believed that both the IPCW and 2-stage methods have advantages and disadvantages, but overall the 2-stage method is the most appropriate for decision-making. The committee concluded that the company's 2-stage method results were appropriate for decision-making.

Pembrolizumab improves overall survival, but not progression-

free survival, in the full trial population

3.7 Pembrolizumab statistically significantly improved the overall survival of people compared with the investigator's choice of docetaxel, paclitaxel or vinflunine. Median survival was 10.3 months (95% confidence interval [CI] 8.0 to 11.8) for pembrolizumab and 7.4 months (95% CI 6.1 to 8.3) for investigator's choice of chemotherapy, with a hazard ratio of 0.73 (95% CI 0.59 to 0.91). However, there was no difference seen for progression-free survival, with a hazard ratio of 0.98 (95% CI 0.81 to 1.19). Also, the Kaplan–Meier plot for progression-free survival was skewed, with pembrolizumab being less clinically effective than the investigator's choice of chemotherapy initially. This was reflected in the median time to progression of 2.1 months (95% CI 2.0 to 2.2) for pembrolizumab and 3.3 months (95% CI 2.3 to 3.5) for the investigator's choice of chemotherapy, but progression then appears to plateau for people on pembrolizumab. The committee was aware that pembrolizumab works by inhibiting the PD-L1 pathway, and that there are some people whose disease will not respond to treatment, and others for whom immunotherapy will delay progression. The committee noted that the objective response rate was 21.1% (95% CI 16.4 to 26.5) for pembrolizumab and 11.4% (95% CI 7.9 to 15.8) for the investigator's choice of chemotherapy. The committee concluded that, in the full trial population, pembrolizumab improves overall survival but does not appear to improve progression-free survival.

Pembrolizumab is more clinically effective than docetaxel or paclitaxel

3.8 The clinical effectiveness results for the post-hoc subgroup analysis of pembrolizumab compared with UK standard care (docetaxel and paclitaxel), and the overall survival results adjusted using the 2-stage method, are academic in confidence and cannot be reported here. The committee noted that a pre-specified subgroup analysis from the full trial shows that the hazard ratios for overall survival and progression-free survival when docetaxel, paclitaxel and vinflunine were analysed alone were similar. Also, it expected that adjusting for treatment switching would improve the results if pembrolizumab is more clinically effective than chemotherapy. The committee concluded that, because of the significant improvements in overall survival, pembrolizumab is more clinically effective than docetaxel or paclitaxel.

Pembrolizumab appears more clinically effective in people whose disease is PD-L1-positive

3.9 Pembrolizumab works by inhibiting the PD-L1 pathway and could be more effective in patients with higher levels of PD-L1 expression. The company defined PD-L1 expression in KEYNOTE-045 by combined proportion score, which includes PD-L1 expression in both the solid tumour and the infiltrating immune cells. The company presented evidence in a PD-L1-positive group (combined proportion score of 1% or more) and a PD-L1 strongly positive group (combined proportion score of 10% or more). The hazard ratios for overall survival and progression-free survival for pembrolizumab compared with the investigator's choice of docetaxel, paclitaxel or vinflunine in the PD-L1 subgroups were respectively 0.61 (95% CI 0.43 to 0.86) and 0.91 (95% CI 0.68 to 1.24) for the PD-L1-positive group, and 0.57 (95% CI 0.37 to 0.88) and 0.89 (95% CI 0.61 to 1.28) for the PD-L1 strongly positive group. The committee concluded that pembrolizumab could be more clinically effective the greater the expression of PD-L1, and that this is biologically plausible considering pembrolizumab's mechanism of action.

Indirect comparison

An indirect comparison of pembrolizumab with best supportive care is not useful for decision-making

3.10 There was no direct trial evidence comparing pembrolizumab with best supportive care. The company's systematic review identified a study comparing vinflunine plus best supportive care with best supportive care alone. The company stated that because the KEYNOTE-045 treatments were not given with best supportive care, a completed network could not be constructed to indirectly compare pembrolizumab and best supportive care. The ERG disagreed that a completed network could not be constructed, because the vinflunine comparator in KEYNOTE-045 could be assumed to include best supportive care. However, the ERG highlighted that an indirect comparison would be inappropriate because the performance status of people in the trials would be much better than in people having best supportive care in clinical practice. The committee recalled that a minority of people would have best supportive care if an active treatment could not be tolerated or if they chose to have it (see section 3.4), but concluded that an indirect comparison using these

trials would not be useful for decision-making. The committee noted that there was no evidence for people who would be likely to have best supportive care, and therefore concluded that it was unable to make a recommendation for this population.

Adverse events

Pembrolizumab is well tolerated in clinical practice

3.11 The clinical experts explained that in their experience of using pembrolizumab, it is well tolerated and associated with fewer severe adverse events than chemotherapy. However, the committee understood that pembrolizumab is associated with some rare but unpleasant and potentially serious adverse events that are specific to immunotherapy. Because only adverse events with an incidence of over 5% were included in the economic model, these rare adverse events associated with immunotherapy were not included in the company's original submission. In its response to consultation the company submitted an updated economic model that explored the impact of including the costs of all serious adverse events. The committee noted that the impact was minimal, and concluded that the company's original approach was appropriate for decision-making.

Assumptions used in the economic model

A 2-year stopping rule for pembrolizumab is appropriate

3.12 In the KEYNOTE-045 protocol the maximum pembrolizumab treatment duration was 2 years from the date of the first dose, at which point treatment must be stopped. This stopping rule was reflected in the company's economic model, but not in the summary of product characteristics which states that treatment should continue until disease progression or unacceptable toxicity. The committee understood that for pembrolizumab for other indications, NICE guidance has included a recommendation to stop treatment after a defined period of time. The Cancer Drugs Fund clinical lead explained that he was confident that a 2-year stopping rule would be acceptable to both patients and clinicians and would be implementable from a commissioning perspective. He noted that if NHS trusts continue treatment beyond 2 years for individual patients, NHS England would not reimburse them for this non-commissioned use of the drug. The committee concluded that incorporating a 2 year stopping

rule in its decision-making was appropriate.

A Weibull curve is the most appropriate to model progression-free survival

3.13 The company and ERG's original preferred model included an exponential curve to model progression-free survival. In its response to consultation the company submitted a new model incorporating an additional 4 months' KEYNOTE-045 data and using a Gompertz curve. The company did not provide a justification for this change. The ERG highlighted that, with the Gompertz curve, the model assumes that after year 6 no one can be in the post-progression state, and people could only move directly from the pre-progression state to death. The ERG preferred using the Weibull curve, because it believed this had the most plausible balance of pre-progression and post-progression survival benefits. The committee acknowledged that using the Gompertz curve results in implausible health state transitions. It noted that the Weibull curve chosen by the ERG is slightly more favourable to pembrolizumab than the original exponential curve, and concluded that the Weibull curve was appropriate to use in its decision-making.

A piecewise model is appropriate, but the best time to switch to a parametric curve is uncertain

3.14 The company and ERG's preferred model used a piecewise approach to model overall survival, in which Kaplan–Meier data are used initially before switching to a parametric curve. This is because the cumulative hazard plot shows that the hazards cross and therefore the proportional hazards assumption does not hold. The ERG and company disagreed at what point the Kaplan–Meier data should switch to a parametric curve. The company considered that week 40 was most appropriate because at this point the cumulative hazards are consistently moving apart. The ERG suggested that week 24 would be more appropriate. This is because this time point is closer to the point at which the cumulative hazards cross, maximising the data for extrapolation, and it believed the hazards were consistent from this point. The committee agreed that it was clear the proportional hazards assumption does not hold. It noted that the long-term variation between different fully-fitted parametric curves was low but that they substantially underestimated long-term overall survival. The committee considered a piecewise model was the most appropriate approach to

extrapolation. It concluded that using either time point to extrapolate the trial data could be plausible and it was unable to judge the most appropriate time point for decision-making. The committee therefore considered both time points in its decision-making.

There are several plausible overall survival extrapolation curves

3.15 The company preferred a log-normal parametric curve to extrapolate pembrolizumab overall survival. The justification was that extrapolations using the Gompertz or generalised gamma curves, which in the original model best fitted the data statistically, resulted in over-optimistic 5-year survival rates for the UK standard care arm (24.3% and 17% in the original model respectively). The company found Cancer Research UK data which identified a 5-year overall survival of 9% to 11% for people with metastatic disease. The log-normal curve had the best statistical fit of the curves closest to the Cancer Research UK 5-year overall survival estimate. The ERG identified several issues with the Cancer Research UK data. People in KEYNOTE-045 had prior chemotherapy whereas the Cancer Research UK population were identified at diagnosis of metastatic disease, and would be having first-line therapy. Also, little is known about the baseline characteristics of the Cancer Research UK population, and so the ERG had reservations about using this data as a reference point. The ERG asked for expert clinical opinion, which suggested a 5-year survival of 2% to 3%. This was in line with systematic review data. On this basis the ERG chose a log-logistic curve which, of the curves closest to their preferred 5-year survival estimate, had the best statistical fit to the pembrolizumab arm. The clinical experts explained that UK clinical practice varies, and the long-term survival of people with metastatic disease is not well known as a result. They would expect the overall survival to be within the range of estimates used by the ERG and the company. The committee concluded that the long-term survival was uncertain, and that it would consider both the company and ERG's preferred overall survival extrapolation in its decision-making.

A lifetime treatment effect is implausible

3.16 The committee recalled that a 2-year stopping rule was incorporated into KEYNOTE-045 and the company's economic model (see section 3.12). The committee noted that there were no data from KEYNOTE-045 on the impact of implementing the stopping rule, because the longest follow-up was only 20.8 months in the original model. The company assumed in its base case that

pembrolizumab remains effective irrespective of time off treatment or implementation of a stopping rule. However, it supplied scenarios in which the hazard ratio for overall survival was set to 1 at different time points to model stopping of the continued treatment effect. The committee was aware that the duration of continued treatment effect after implementation of a stopping rule is an area of uncertainty for new immunotherapies, but it concluded that a lifetime continued treatment effect was implausible.

Utility estimates should be based on progression state

3.17 EQ-5D data were collected directly in KEYNOTE-045; these data are the preferred measure of health-related quality of life in adults. For the company's base case, utility values for pembrolizumab and UK standard care were pooled (adjusted for age) and divided into 5 groups based on time to death (from less than 30 days to at least 360 days). However, the ERG highlighted that the utilities were inconsistent, with utilities in the UK standard care arm often higher than in the pembrolizumab arm. They were also implausibly high, with the utilities at 360 days before death similar to the UK population norm for people of the same age. There was also concern about the small sample sizes when splitting the data into many groups, with only 14 responses in the UK standard care arm at less than 30 days before death. Also, how the company approached the issue of missing data in the different groups was not fully addressed. The ERG preferred to use utility values which corresponded to a pre-progression and post-progression state, and also used a more recent algorithm to incorporate age-related disutility. The committee recognised that the company's preferred time to death approach to modelling utilities was capable of describing the diminishing quality of life after progression in a way that the progression-based utilities could not. However, it considered that the overall validity of those estimates was questionable considering the implausibly high values, small sample sizes and missing data. It agreed with the ERG's rationale and concluded that utilities should be based on progression state, and the more recent age-related disutility algorithm should be used.

Utility estimates should exclude the vinflunine data

3.18 The company preferred to include the vinflunine data to maximise the utility data for the model. The ERG suggested that the vinflunine data should be removed, because vinflunine is not used in clinical practice and is not included in the survival data. The committee agreed with the ERG's rationale and concluded

that the vinflunine data should not be included in the utility estimates.

Utility estimates should be pooled across treatment arms

3.19 The company preferred to pool the utilities across all treatments because there were no statistically significant or clinically meaningful differences between the pembrolizumab and UK standard care arms when utilities were valued using the time to death approach. However, in its response to consultation the company stated that if utilities are based on progression state, they should be treatment specific because the pembrolizumab utilities are significantly higher than for UK standard care, and the difference is clinically meaningful. The ERG stated that the company's rationale was inconsistent because any differences in utilities between pembrolizumab and UK standard care should be evident in both approaches. The ERG further noted that treatment-specific utilities are favourable to pembrolizumab when the utilities are based on progression state, but not when the utilities are based on time to death. The ERG highlighted that KEYNOTE-045 was open-label, which results in a risk of bias to the utilities because they are a patient-reported outcome. In addition, any major differences to patient experience would be captured by the adverse event disutility. This is because the adverse event frequency was calculated per treatment arm, and if the magnitude of adverse event disutility was also calculated separately by treatment arm this would be marginally unfavourable to pembrolizumab. The ERG therefore preferred to pool the utilities. The committee recalled that the utilities using the time to death approach were inconsistent (see section 3.17), which it considered supported pooling the utilities. It agreed that the contradictory results seen using unpooled utilities for the time to death approach and the progression-based approach were unexpected. The committee considered that, given the uncertainties raised about treatment-specific utilities, the utilities should be pooled across treatment arms. The committee was reassured that differences between the treatments may be partly captured by the adverse event disutility.

Cost-effectiveness estimates

The company proposed pembrolizumab for the Cancer Drugs Fund

3.20 The company submitted a proposal for the committee to consider

pembrolizumab for the Cancer Drugs Fund rather than routine commissioning and proposed a confidential commercial access agreement for pembrolizumab within the Cancer Drugs Fund. The committee considered the incremental cost-effectiveness ratios (ICERs) based on this commercial offer in its decision-making. The committee understood that it was not considering pembrolizumab for routine use, and discussed the new arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting the addendum to the NICE process and methods guides.

The most plausible ICER is higher than the ERG's preferred ICER

3.21 The company's deterministic ICER was £41,004 per quality-adjusted life year (QALY) gained compared with docetaxel or paclitaxel, whereas the ERG's preferred deterministic ICER was £44,504 per QALY gained. The ERG's changes to the company's base case:

- excluded the vinflunine data from the utilities (see section 3.18)
- pooled utilities across treatment arms by progression state (see sections 3.17 and 3.19)
- used an updated algorithm to calculate age-related disutility (see section 3.17)
- changed the proportion of people having docetaxel and paclitaxel to UK market share
- used a Weibull parametric curve to extrapolate progression-free survival (see section 3.13)
- extrapolated the overall survival trial data at 24 weeks (see section 3.14) and
- used a log-logistic parametric curve to extrapolate overall survival (see section 3.15).

The committee noted that changing the proportion of people having docetaxel and paclitaxel to the UK market share had a negligible effect on the ICER, but was a reasonable change. It agreed with all the ERG's preferred assumptions for the utilities. The committee recalled that it considered the time point at which to extrapolate the trial data, and the specific extrapolation curve to use, to be uncertain (see sections 3.14 to 3.15). It noted that when using the company's preferred overall survival extrapolation the ICER increased from £44,504 to £46,447 per QALY gained. The committee highlighted that the ERG's preferred log-logistic extrapolation curve,

- extrapolated from 40 weeks (instead of 24 weeks), would have a plausible 5-year overall survival rate of 7.8% for the UK standard care arm and would result in an ICER of £54,064 per QALY gained. Also, the committee recalled that the economic models assume an implausible lifetime continued treatment effect (see section 3.16). Including a reduced continued treatment effect would increase the ICER further and the committee highlighted that the ICER is sensitive to this assumption. Using the ERG's preferred overall survival extrapolation, scenarios which assume no continued treatment effect after 3 or 5 years increase the ICER by £12,956 and £6,182 per QALY gained respectively. Therefore the committee concluded that the most plausible ICER was uncertain, but it was confident that it would be higher than the ERG's preferred ICER of £44,504 per QALY gained. The committee noted that because the ICER was sensitive to the assumptions where there was uncertainty it was plausible that the ICER was higher than the ERG's preferred ICER.

The ICER is most sensitive to the overall survival extrapolation

3.22 The committee noted that the probabilistic ICERs were consistent with the deterministic results. However, the committee highlighted that the tornado diagram showed that the parameters of the survival extrapolation had the greatest impact on the variation of the probabilistic sensitivity analysis. The committee recalled that there is uncertainty in the most plausible long-term overall survival (see section 3.15), and the tornado diagram reinforced the committee's view that the overall survival extrapolation is uncertain.

PD-L1 subgroups

Cost-effectiveness analyses based on PD-L1 expression are not useful for decision-making

3.23 Pembrolizumab works by inhibiting the PD-L1 protein and appeared, from the KEYNOTE-045 results, to be more clinically effective in people with higher levels of PD-L1 expression (see section 3.9). The committee considered that it was therefore possible that pembrolizumab might be more cost effective in this group. The company presented cost-effectiveness results for the PD-L1 subgroups, but the results are academic in confidence and cannot be reported here. The committee judged that the cost-effectiveness results for the subgroups were inconsistent with the evidence seen in KEYNOTE-045, and did not find them plausible. Therefore the committee did not consider the company's cost-effectiveness results to be reliable for decision-making and

concluded that it could only make a recommendation for the whole population.

End of life

Life expectancy for people with urothelial carcinoma is less than 24 months

3.24 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's Cancer Drugs Fund technology appraisal process and methods. For people with locally advanced or metastatic disease who have had platinum-containing chemotherapy, data from the company's model and from the literature showed that median overall survival was much less than 24 months for people having treatment with UK standard care. The clinical experts also agreed that they would expect people with locally advanced or metastatic urothelial carcinoma to live for less than 24 months. The committee concluded that the short life expectancy criterion was met.

Pembrolizumab extends life by at least 3 months, and meets the criteria for end-of-life treatments

3.25 The committee noted that the median overall survival for pembrolizumab in KEYNOTE-045 was 10.3 months (95% CI 8.0 to 11.8) compared with 6.9 months (95% CI 5.3 to 8.1) for UK standard care (using a 2-stage method for adjustment). The company's economic model estimated that, using the company's preferred overall survival extrapolation, the mean survival with pembrolizumab was 33.7 months compared with 19.5 months with UK standard care. The committee concluded that pembrolizumab would extend life by more than 3 months, and therefore met the end-of-life criteria.

Conclusion

Pembrolizumab is recommended within the Cancer Drugs Fund

3.26 When using the committee's preferred assumptions, the ICERs including the company's or ERG's preferred overall survival extrapolations were lower than would normally be considered cost effective for end-of-life treatments; ICERs of £46,447 and £44,504 per QALY gained respectively. However, the committee recalled that other plausible extrapolation scenarios produced higher ICERs,

and that all the ICERs assumed an implausible lifetime continued treatment effect (see section 3.21). The committee considered that pembrolizumab has plausible potential to be cost effective based on the evidence. It acknowledged that immature data were used in the model and that ongoing data collection in KEYNOTE-045 would reduce the uncertainty surrounding the overall survival extrapolation and the magnitude of any continued treatment effect. Therefore the committee concluded that pembrolizumab was suitable to be recommended for use in the Cancer Drugs Fund for people with locally advanced or metastatic urothelial carcinoma who have had platinum-containing chemotherapy.

Other factors

3.27 No equality issues were identified.

3.28 The company did not highlight any additional benefits that had not been captured in the QALY calculations.

4 Implementation

4.1 When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, NHS England will make it available within the conditions of the managed access agreement. This means that, if a patient has locally advanced or metastatic urothelial carcinoma that has previously been treated with platinum-containing chemotherapy and the doctor responsible for their care thinks that pembrolizumab is the right treatment, it should be available for use, in line with NICE's recommendations and the Cancer Drugs Fund criteria in the managed access agreement. Further information can be found in NHS England's Appraisal and Funding of Cancer Drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance when the drug or treatment, or other technology, is approved for use within the Cancer Drugs Fund. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, for use within the Cancer Drugs Fund, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal determination or agreement of a managed access agreement by the NHS in Wales, whichever is the latter.

4.3 Pembrolizumab has been recommended according to the conditions in the managed access agreement. As part of this, NHS England and Merck Sharp & Dohme have a commercial access agreement that makes pembrolizumab available to the NHS at a reduced cost. The financial terms of the agreement are commercial in confidence. Any enquiries from NHS organisations about the commercial access agreement should be directed to keiron.hughes@merck.com.

5 Recommendations for data collection

5.1 As a condition of the positive recommendation and the managed access agreement, the company is required to collect efficacy data from the KEYNOTE-045 study.

6 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 D.

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.

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.

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Accreditation