NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using pembrolizumab in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: July 2017

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination.
- Subject to any appeal by consultees, the final appraisal determination may be used as the basis for NICE's guidance on using pembrolizumab in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 24 August 2017

Second appraisal committee meeting: 30 August 2017

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Pembrolizumab is not recommended, within its anticipated marketing authorisation, for treating locally advanced or metastatic urothelial carcinoma in adults who have had prior platinum-containing chemotherapy.

1.2 This recommendation is not intended to affect treatment with pembrolizumab that was started in the NHS before this guidance was published. Adults 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

Clinical trial evidence shows that pembrolizumab significantly improves overall survival compared with docetaxel and paclitaxel (the current treatment options for people with locally advance or metastatic urothelial carcinoma).

Pembrolizumab meets NICE's criteria to be considered a life-extending treatment at the end of life. Life expectancy for people with locally advanced or metastatic urothelial carcinoma is less than 24 months. Pembrolizumab is likely to extend people's lives by more than 3 months.

The most likely cost-effectiveness estimate is uncertain because the most appropriate methods and assumptions for the economic modelling are unclear. However, all plausible estimates are higher than what NICE normally considers acceptable for end-of-life treatments, that is, £50,000 per quality-adjusted life year (QALY) gained. There are also other plausible scenarios and assumptions not fully accounted for which would increase the estimate further. Therefore, pembrolizumab is not recommended.

The cost effectiveness of pembrolizumab was also considered only for people with urothelial carcinoma expressing the PD-L1 protein because it appears to be more effective in this group than in people who do not express PD-L1. However, the results were not reliable so no recommendations for this group can be made.

Pembrolizumab was considered for use in the Cancer Drugs Fund but cannot be recommended because it does not have the potential to be cost effective.

2 The technology

Pembrolizumab (Keytruda, Merck Sharp & Dohme)	
Anticipated marketing authorisation	On 20 July 2017 the Committee for Medicinal Products for Human Use adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product pembrolizumab, indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.
Recommended dose and schedule	200 mg every 3 weeks until disease progression or unacceptable toxicity.
Price	£2,630 per 100 mg vial (excluding VAT; company submission). The company has agreed a patient access scheme with the Department of Health. If pembrolizumab had been recommended, this scheme would provide a simple discount to the list price of pembrolizumab with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

3 Committee discussion

The appraisal committee (section 5) 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 places 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. The committee 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 had no 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-based 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 proposed marketing authorisation for pembrolizumab includes people for whom cisplatin is unsuitable and people who have had previous platinum-based chemotherapy. The company proposed that this appraisal focuses on the population who have had platinum-based chemotherapy, because this reflects the trial evidence currently available. The committee heard that the company plans to address the remainder of the marketing authorisation population 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 which evidence has been presented.

Comparators

Paclitaxel, docetaxel and best supportive care are relevant comparators for people who have had platinum-based 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 treatment with 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 in the future, 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 NHS England 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 KEYNOTE-045, an open-label, randomised controlled trial. 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 committee heard from clinical experts and the ERG 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 committee heard from the company 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. The committee was aware that using post-hoc subgroup analyses introduces the risk of bias, and that excluding vinflunine data reduces the statistical power of the trial. But it 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/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, generates artificial survival times for those who switch, and assumes a common treatment effect for switchers; whereas people in KEYNOTE-045 were able to switch to a range of anti-PD-L1/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 is skewed, with pembrolizumab being less clinically effective than the investigator's choice of chemotherapy initially. This is 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 investigator 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 investigator's choice of paclitaxel, docetaxel or vinflunine. The committee concluded that in the full trial population treatment with 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 of 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 between docetaxel, paclitaxel and vinflunine when analysed alone are similar. Also, it would expect 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 who are PD-L1-positive

3.9 The committee was aware that 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 overall survival for 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 for pembrolizumab compared 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 also 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 choose 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 it concluded they were 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. The committee noted that, 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 submission.

Assumptions used in the economic model

A 2 year stopping rule for pembrolizumab is appropriate

3.12 The committee noted that 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 is reflected in the company's economic model, but not in the anticipated summary of product characteristics which states that treatment should continue until disease progression or unacceptable toxicity. The committee understood that for pembrolizumab in other indications, NICE guidance has included a recommendation to stop treatment after a defined period of time. The committee heard from NHS England that it

was confident that a 2 year stopping rule would be acceptable to both patients and clinicians and would be implementable from a commissioning perspective. NHS England further stated that, if NHS trusts continue treatment beyond 2 years for individual patients, NHS England will 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 piecewise model is appropriate, but the best time to switch to a parametric curve is uncertain

3.13 The company and ERG's preferred model uses a piecewise approach, 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 hazard 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 a cut-off at week 16, the point at which the cumulative hazards cross, would be more appropriate. This is because it believed the hazards were consistent and this would maximise the data for extrapolation. However the ERG was unable to explore a 16-week cut-off in the company's economic model and instead chose week 24 because this was the next cut-off point the economic model allowed. The committee agreed that it was clear the proportional hazard 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 both time points at which to extrapolate the trial data could be plausible and was unable to make a

judgement on 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

3.14 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 best fitted the data statistically, resulted in over-optimistic 5-year survival rates for the UK standard care arm (24.3% and 17% 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 closest 5-year overall survival to this, at 7.8%. 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 patients who have generated the Cancer Research UK data, 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%, which also corresponded to data found in a systematic review. On this basis the ERG chose a log-logistic curve which has a 5-year overall survival rate of 3.2%. The committee heard from clinical experts that there is variation in clinical practice in the UK, 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 company. The committee concluded that the long-term survival was uncertain, and that there are several curves using both the ERG and the company's preferred cut-off which would result in plausible long-term survival estimates.

A lifetime treatment effect is implausible

3.15 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. 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 is an area of uncertainty for new immunotherapies, but it concluded a lifetime continued treatment effect to be implausible.

Utility estimates should be based on progression state

3.16 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 implausibly high and the values at 360 days before death were 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, and how the company approached the issue of missing data in the different groups, which was not addressed. The ERG preferred to use utility values which correspond to a pre-progressed and progressed state, and also used a more recent algorithm to incorporate age-related disutility. The committee 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 vinflunine data and be pooled across treatment arms

3.17 The committee noted that the company preferred to include vinflunine data to maximise the data for the model, and pooled the data across all treatments because there were no statistically significant or clinically meaningful differences between the pembrolizumab and UK standard care arms. The ERG suggested that the vinflunine data should be removed, because vinflunine is not used in clinical practice and is removed in the survival data. The ERG disagreed that there was no statistically significant difference between the arms, because pembrolizumab has significantly higher utilities compared with UK standard care when basing utilities on progression state. However the ERG noted that KEYNOTE-045 was open-label, which results in a high risk of bias to the utilities, and therefore also preferred to pool the utilities. The committee agreed with the ERG's rationale and concluded that the vinflunine data should not be included and the utilities should be pooled across treatment arms.

Cost-effectiveness estimates

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

3.18 The company's deterministic base-case incremental cost-effectiveness ratio (ICER) was £45,833 per quality-adjusted life year (QALY) gained compared with docetaxel or paclitaxel, whereas the ERG's preferred deterministic ICER was £51,235 per QALY gained. The ERG's changes to the company's base case were:

- excluding the vinflunine data from utilities (see section 3.17)
- pooling utilities across treatment arms by progression state (see sections 3.16 to 3.17)

- using an updated algorithm to calculate age-related disutility (see section 3.16)
- changing the proportion of people having docetaxel and paclitaxel to UK market share
- using a cut-off point of 24 weeks at which to extrapolate the overall survival trial data (see section 3.13)
- using a log-logistic parametric curve to extrapolate overall survival (see section 3.14).

The committee noted that the ERG's change to 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. The committee agreed with all the ERG's preferred assumptions for the utilities. The committee noted that combining these assumptions increases the company's base-case ICER from £45,833 to £55,407 per QALY gained. 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 highly uncertain (see sections 3.13 to 3.14). The committee noted that the ICER is very sensitive to the choice of curve and the time point used, with an ICER range of £33,092 to £295,841 per QALY gained using a 24-week time point using the rest of the ERG's preferred assumptions, and a range of £55,118 to £101,593 per QALY gained at the 40-week time point for extrapolation. The committee highlighted that the ERG's preferred log-logistic extrapolation curve, at the 40-week cut-off, would have a plausible 5-year overall survival rate for the UK standard care arm of 7.1% and would result in an ICER of £70,304 per QALY gained. Also, the committee recalled that the economic models exclude rare but potentially serious adverse events that are specific to immunotherapy (see section 3.11) and assume an implausible lifetime continued treatment effect (see section 3.15). Including these adverse events and a reduced continued

treatment effect would increase the ICER further and the committee highlighted that a scenario which assumes no continued treatment effect after 5 years increases the company's base-case ICER by around £6,000 per QALY gained. Therefore the committee concluded that the most plausible ICER was highly uncertain, but it was confident that it would be substantially higher than the ERG's preferred ICER of £51,235 per QALY gained.

The ICER is most sensitive to the overall survival extrapolation

3.19 The probabilistic sensitivity analyses submitted by the company increased its base-case ICER slightly to £46,194 per QALY gained. The ERG's probabilistic analysis decreased its base-case ICER slightly to £50,902 per QALY gained. The committee noted that whereas the probabilistic ICERs were consistent with the deterministic results, the tornado diagram highlighted that the parameters of the survival extrapolation had the greatest impact on the variation of the probabilistic sensitivity analysis, with the 4 top results corresponding to overall survival extrapolation parameters. The committee recalled that there is uncertainty in the most plausible long-term overall survival (see section 3.14), and the tornado diagram reinforces the committee's view that the overall survival extrapolation is highly uncertain.

PD-L1 subgroups

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

3.20 The committee was aware that pembrolizumab works by inhibiting the PD-L1 protein and therefore it may be more cost effective in people with higher levels of PD-L1 expression. It recalled that pembrolizumab appeared to be more clinically effective in people with higher levels of PD-L1 expression. The committee considered that it was therefore possible

that pembrolizumab might be more cost effective in these groups. The committee recalled that KEYNOTE-045 reported results of a PD-L1-positive subgroup (combined proportion score of 1% or more) and a PD-L1 strongly positive subgroup (combined proportion score of 10% or more), and that it appeared that pembrolizumab was more clinically effective in people whose tumours are PD-L1 strongly positive (see section 3.9). 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

3.21 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 previous 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 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 population met the short life expectancy criterion.

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

3.22 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 committee noted that the company's economic model estimated that the mean number of months of life with pembrolizumab is 32.5 months compared with 19 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 not recommended for routine use in the NHS for previously treated urothelial carcinoma

3.23 The committee concluded that the most plausible ICERs (see section 3.18) were higher than those usually considered a cost-effective use of NHS resources, even for end-of-life treatments. The cost-effectiveness evidence was highly uncertain because the committee was unable to make a judgement on the most appropriate overall survival extrapolation to use, and the ICER is highly sensitive to this parameter. The committee was unable to make a judgement on the cost effectiveness of pembrolizumab for people who were PD-L1 positive, because the subgroup analyses were unreliable. The committee did not recommend pembrolizumab for routine use in the NHS for people with previously treated locally advanced or metastatic urothelial carcinoma.

Cancer Drugs Fund

Pembrolizumab is not recommended through the Cancer Drugs Fund

3.24 Having concluded that pembrolizumab could not be recommended for routine use, the committee then considered if it could be recommended for treating locally advanced or metastatic urothelial carcinoma within the

Cancer Drugs Fund. The committee 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 committee heard from the company that it preferred pembrolizumab to be made available via routine commissioning.

3.25 When using the committee's preferred assumptions, the ICERs including the company's or ERG's preferred extrapolations are both higher than would normally be considered cost effective for end-of-life treatments; with ICERs of £55,407 and £51,235 per QALY gained respectively. The committee recalled that other plausible extrapolation scenarios produced significantly higher ICERs, and that all the ICERs assumed an implausible lifetime continued treatment effect (see section 3.18). The committee considered that there was no plausible potential that pembrolizumab would be cost effective in the full population based on the evidence. It acknowledged that the data used in the model were immature, with a median follow-up of around 10 months for people in the pembrolizumab arm, and that ongoing data collection in KEYNOTE-045 would reduce the uncertainty surrounding the overall survival extrapolation. However, because pembrolizumab was not plausibly cost effective, the committee concluded that it was not suitable to be recommended for use in the Cancer Drugs Fund for previously treated disease.

Other factors

3.26 No equality issues were identified.

3.27 The Pharmaceutical Price Regulation Scheme (2014) payment mechanism was not relevant in considering the cost effectiveness of pembrolizumab.

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

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Gary McVeigh
Chair, appraisal committee
July 2017

5 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.

Thomas Strong

Technical Lead

Christian Griffiths

Technical Adviser

Kate Moore

Project Manager

ISBN: [to be added at publication]