

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final appraisal document

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

1 Recommendations

- 1.1 Pembrolizumab is not recommended, within its marketing authorisation, for treating locally advanced or metastatic urothelial carcinoma in adults who have had platinum-containing chemotherapy.
- 1.2 This recommendation is not intended to affect treatment with pembrolizumab that was started in the Cancer Drugs Fund before this guidance was published. For those people, pembrolizumab will be funded by the company until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Pembrolizumab for previously treated locally advanced or metastatic urothelial carcinoma was available in the Cancer Drugs Fund in [technology appraisal 519](#). This appraisal reviews the evidence collected through the Cancer Drugs Fund on pembrolizumab. Pembrolizumab cannot stay in the Cancer Drugs Fund for this indication after the evidence is reviewed.

Treatment for previously treated locally advanced or metastatic urothelial carcinoma includes docetaxel or paclitaxel. Clinical trial evidence shows that pembrolizumab significantly improves overall survival compared with docetaxel and paclitaxel. Some evidence has also been collected through the Cancer Drugs Fund.

Atezolizumab is now also a possible treatment. But it was not established clinical practice in the NHS at the time of the original appraisal, so is not included in the scope for this review.

If an active treatment is not tolerated or people choose not to have it, best supportive care is given. No clinical or cost-effectiveness evidence was available for pembrolizumab compared with best supportive care.

Pembrolizumab meets NICE's criteria to be considered a life-extending treatment at the end of life. The most likely cost-effectiveness estimate for pembrolizumab is uncertain. This is because it is not clear which model of overall survival is most appropriate or how long the treatment benefit of pembrolizumab should continue. Even when pembrolizumab is offered with its agreed discount, the most plausible cost-effectiveness estimate remains above what NICE normally considers acceptable for end-of-life treatments. Therefore, pembrolizumab is not recommended.

2 Information about pembrolizumab

Marketing authorisation indication

1.3 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

1.4 Intravenous infusion of 200 mg every 3 weeks, or 400 mg by intravenous infusion every 6 weeks, until disease progression or unacceptable toxicity.

Price

1.5 £2,630 per 100 mg vial (excluding VAT; company submission).

- 1.6 The company has a commercial arrangement. This makes pembrolizumab available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.
- 1.7 While available in the Cancer Drugs Fund (see technology appraisal 519), pembrolizumab has a commercial arrangement (managed access agreement including a commercial access agreement).

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), and the technical report developed through engagement with stakeholders. See the [committee papers](#) for full details of the evidence.

The committee recognised that there were remaining areas of uncertainty in the analyses presented (see technical report, table 2, page 37), and took these into account in its decision making. It discussed issues 1 to 5 from the technical report, which were not resolved after technical engagement:

- choice of extrapolation for progression-free survival
- treatment switching
- choice of extrapolation curve and cut-off point for overall survival
- treatment effect duration
- PD-L1 expression subgroups.

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 effect 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 and comparators

Paclitaxel, docetaxel and best supportive care are the relevant comparators for this appraisal

- 3.2 The committee was aware that the treatment pathway for locally advanced or metastatic urothelial carcinoma had changed since the original appraisal of pembrolizumab for this indication. This is because of [NICE's technology appraisal guidance on atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy](#). Atezolizumab was not established clinical practice in the NHS when the final scope for the original appraisal of pembrolizumab was issued. In a review of a drug funded by the Cancer Drugs Fund, no changes to the final scope of the original appraisal are allowed, so atezolizumab could not be included as a comparator (see section 6.25 of the [NICE guide to the processes of technology appraisal](#)). At the time of the original appraisal of pembrolizumab, first-line treatment for locally

advanced or metastatic disease was usually a platinum-containing chemotherapy regimen. For people who were not well enough or chose not to have this, best supportive care was offered. Retreatment with a first-line chemotherapy was also included in the scope for the original appraisal of pembrolizumab. However, it was not established clinical practice then, because retreatment was used before a second-line treatment option was available. Also, most clinicians would have used a taxane (paclitaxel and docetaxel). The committee agreed that treatment options for people with disease progression after platinum-containing chemotherapy at that time included docetaxel, paclitaxel or best supportive care. The committee concluded for the original appraisal that the most relevant comparators were paclitaxel, docetaxel and best supportive care.

The KEYNOTE-045 post-hoc subgroup results are most appropriate for decision making

3.3 The clinical effectiveness evidence for pembrolizumab came from KEYNOTE-045, an open-label, randomised controlled trial. It included people with disease progression or recurrence of urothelial cancer after treatment with a platinum-containing regimen (cisplatin or carboplatin). The comparator arm in the trial was 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. This included:

- 188 people randomised to have pembrolizumab
- 182 people randomised to have the investigator's choice of paclitaxel or docetaxel (referred to as the 'UK standard of care [UK SoC]' control arm).

The committee concluded that the trial was good quality and the results were informative for decision making. It was aware that using post-hoc

subgroup analyses introduced 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 UK clinical practice and is the most appropriate evidence for decision making.

Pembrolizumab improves overall survival compared with docetaxel or paclitaxel

3.4 In KEYNOTE-045, progression-free survival and overall survival were co-primary end points. In the latest data cut of KEYNOTE-045, the median overall survival for pembrolizumab was 10.1 months (95% confidence interval [CI] 7.6 to 12.9) compared with 6.2 months (95% CI 5.2 to 7.4) for the UK SoC arm with a hazard ratio of 0.64 (95% CI 0.49 to 0.81). This suggests that pembrolizumab improves overall survival compared with docetaxel or paclitaxel. However, the median progression-free survival for pembrolizumab was 2.1 months (95% CI 2.0 to 2.2) compared with 3.3 months (95% CI 2.3 to 3.5) in the UK SoC arm, with a hazard ratio of 0.95 (95% CI 0.76 to 1.19). The committee concluded that pembrolizumab improves overall survival but does not appear to improve progression-free survival. The additional clinical data collected by Public Health England as part of the Systemic Anti-Cancer Therapy dataset while pembrolizumab was in the Cancer Drugs Fund did not contribute to this review.

The 2-stage method for subsequent immunotherapy in KEYNOTE-045 is appropriate in the original appraisal

3.5 If their disease progressed, people in the trial could have subsequent anti-PD-L1 or PD-1 treatment. This included atezolizumab, avelumab, durvalumab, nivolumab, and pembrolizumab. The company adjusted overall survival in the UK SoC arm to account for these treatments using the 2-stage method to adjust for treatment switching. The 2-stage method used an acceleration factor (a ratio of the survivor function for the pembrolizumab and UK SoC treatment arms). This was to shrink the

survival time of patients who had UK SoC, were eligible for subsequent therapy, and who then had anti-PD-L1 or PD-1 therapy. The ERG believed that the 2-stage method had disadvantages, but overall was the most appropriate. The committee concluded that the company's 2-stage method was appropriate for decision making in the original appraisal.

New KEYNOTE-045 data shows that the 2-stage method may not be appropriate, and the unadjusted method should also be taken into account

3.6 The November 2018 data cut from KEYNOTE-045 showed that the acceleration factor was larger and applied to more people in the trial. This meant the 2-stage adjustment had a greater influence on overall survival than it did in the original appraisal. The acceleration factor was 5.37 (95% CI 3.23 to 10.09) (based on 25 patients) after the November 2018 data cut, compared with 3.86 (95% CI 1.79 to 11.68) (based on 14 patients) using previous data. The ERG considered that both the 2-stage adjusted analyses and analyses without this adjustment for treatment switching should be carefully considered. It advised that the true overall survival benefit would be somewhere between the result of the 2 approaches. Using an approach without the adjustment might overestimate survival time in the UK SoC arm, but the 2-stage method might underestimate survival time in this arm too much. The ERG advised that the main uncertainties with the 2-stage adjustment were:

- The wide confidence interval around the acceleration factor showed a high degree of uncertainty.
- The adjustment method assumed an average adjustment for all people switching to anti-PD-L1 or PD-1 therapy. The ERG considered it unlikely that all patients who switched benefitted equally from the anti-PD-L1 or PD-1 treatment. This was because evidence from KEYNOTE-045 suggested pembrolizumab had less benefit than UK SoC for the first 3 months of follow up, and because immunotherapies have not been shown to benefit everyone.

- With the adjustment, the benefit would have been the same as if patients had anti-PD-L1 or PD-1 therapy earlier in their disease pathway. The KEYNOTE-045 trial data did not support this.
- There was potential for selection bias related to switching, and unmeasured prognostic factors could affect the data.

In response to the appraisal consultation document, the company advised that it considered the updated acceleration factor to be more reliable than the original acceleration factor. This was because it was calculated from a larger sample size and the confidence intervals were narrower and within the range of the originally calculated confidence intervals. The ERG stated that the main concern was not the size of the acceleration factor, but that the increased size meant the adjustment had more influence and so the existing uncertainties associated with the 2-stage method were more important. With the most up-to-date data from November 2018, 40 people on the UK SoC arm of the trial switched to an anti-PD-L1 or PD-1 treatment. The acceleration factor was calculated from the 25 people who switched when progression of their disease was documented. The acceleration factor was not applied to the overall survival time of 15 patients who switched at different times. The ERG stated that the company had not provided an established rule for switching. In response to consultation, the company provided a sensitivity analysis applying the acceleration factor to all 40 patients. In this, the hazard ratio for pembrolizumab compared with UK SoC was 0.55. However, the calculation of the acceleration factor was not adjusted to include these 15 patients. The committee considered that using the 2-stage adjustment for treatment switching likely underestimated the incremental cost-effectiveness ratios (ICERs) but using no adjustment would overestimate the ICERs. It concluded that the true overall survival benefit was probably between that seen with an adjustment for treatment switching and that without an adjustment.

PD-L1 positive subgroups are not clinically distinct

3.7 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 did not present an analysis showing the interaction between treatment effect and PD-L1 status, or results for the PD-L1 negative subgroup using data from the November 2018 cut-off. The committee agreed there was inherent uncertainty when considering estimates of effectiveness based on any subgroup data. The clinical expert explained that PD-L1 is not a predictive biomarker for pembrolizumab after platinum-containing chemotherapy, but it is more relevant for pembrolizumab for people when cisplatin is unsuitable. This is reflected in the marketing authorisation for pembrolizumab in the first-line indication for people when cisplatin is unsuitable, because it specifies PD-L1 expression through combined proportion score level. The clinical expert advised that diagnostic tissue samples for combined proportion score testing are taken before first-line treatment, and combined proportion score may change after platinum-based chemotherapy. This means combined proportion score and PD-L1 expression are not predictive biomarkers in this post-chemotherapy population. The committee agreed that PD-L1 positive subgroups were not clinically distinct subgroups for this indication. It concluded to not consider PD-L1 subgroups in its decision making.

Comparison with best supportive care

No evidence is available comparing pembrolizumab with best supportive care

3.8 The committee considered best supportive care as a relevant comparator, because a few people would have best supportive care if an active treatment was not tolerated or they chose not to have it (see section 3.2). There was no direct trial evidence comparing pembrolizumab with best supportive care. The company did not consider best supportive care a

relevant comparator and, in the original appraisal, did not present any new clinical or cost-effectiveness evidence comparing pembrolizumab with best supportive care. Therefore, the committee concluded it was unable to make a recommendation on this, and agreed not to consider it further.

Adverse events

Pembrolizumab is well tolerated in clinical practice

3.9 Pembrolizumab is associated with some rare but unpleasant, and potentially serious, adverse events that are specific to immunotherapy. The committee understood that pembrolizumab was well tolerated and that patients considered it to have fewer severe adverse events than chemotherapy. The patient experts explained that, although pembrolizumab does have side effects, these are typically less than for chemotherapy for this indication. They suggested that pembrolizumab did not interfere with everyday activities as much. The committee concluded that pembrolizumab was well tolerated.

Assumptions used in the economic model

A 2-year stopping rule for pembrolizumab is appropriate

3.10 In the KEYNOTE-045 protocol, the maximum pembrolizumab treatment duration was 2 years from the first dose, when treatment must be stopped. This was not reflected in the summary of product characteristics, which states that treatment should continue until disease progression or unacceptable toxicity. For pembrolizumab for other indications, and for the [NICE technology appraisal of atezolizumab for treating locally advanced metastatic urothelial cancer after platinum-containing chemotherapy](#), a 2-year stopping rule was applied. The committee noted that the 2-year stopping rule was included in company's economic model, and concluded that it was appropriate.

A Weibull curve is the most appropriate to model progression-free survival in both treatment arms

3.11 In the original appraisal, the committee concluded that the Weibull curve for progression-free survival was appropriate. The committee noted that, for the review, the company still extrapolated progression-free survival from 21 weeks, but preferred a log-normal curve for the pembrolizumab arm. This was based on statistical and visual fit to the KEYNOTE-045 data, and then was used for the UK SoC arm to be consistent. The ERG considered it appropriate to extrapolate from 21 weeks, but only found the Weibull curve to consistently be among the best fitting curves for both the pembrolizumab and the UK SoC arms. This was according to the Akaike information criterion and the Bayesian information criterion. The ERG explained that [NICE's technical support document 14](#) advises that when parametric models are fitted separately to individual treatment arms, the same extrapolation should be used for both arms. Otherwise, substantial justification would be needed to use different extrapolation models. The committee considered the Weibull curve to fit well to the almost-complete data for the UK SoC arm, and also to the 2 to 3-year progression-free survival data for pembrolizumab (the benefit is very uncertain beyond that). The Weibull curve was most consistent with the Kaplan–Meier data seen at 2 and 3 years in both arms of the KEYNOTE-045 trial, and was also a good visual fit. The committee concluded that the Weibull curve was the most appropriate curve to model progression-free survival and that it should be used for both the pembrolizumab and UK SoC arms.

A piecewise model is appropriate to model overall survival, and the best time to switch to a parametric curve is at 24 weeks

3.12 The company used a piecewise approach to model overall survival, in which Kaplan–Meier data are used first before switching to a parametric curve. This is because the cumulative hazard plot showed that the hazards crossed and therefore the proportional hazards assumption did

not hold. The company incorporated switching to a parametric curve at week 24 in its base-case analysis because the cumulative hazard curves started separating from week 24. The committee agreed that the company's piecewise model was appropriate to model overall survival, and the best time for switching to a parametric curve was at 24 weeks.

The long-term effect of a stopping rule on the duration of treatment effect is unknown for immunotherapies, but a lifetime treatment effect is implausible

3.13 A 2-year stopping rule was appropriate for pembrolizumab (see section 3.10). The duration of continued treatment effect after implementation of a stopping rule is an area of uncertainty for all immunotherapies. Before this review, there were no data from KEYNOTE-045 on the effect of implementing the stopping rule, because the longest follow up was only 20.8 months. In the original appraisal, the committee concluded that a lifetime treatment effect was implausible. While a small number of patients could have 'immune memory' after the 2-year stopping point for treatment with pembrolizumab, this was uncertain. The clinical expert explained that the long-term effect of stopping immunotherapy at 2 years was still unknown for any disease.

Evidence of treatment effect duration from other pembrolizumab trials is not appropriate for decision making

3.14 The company highlighted that data supporting a long-term survival benefit was available across the pembrolizumab clinical study programme, particularly from KEYNOTE-001 (melanoma, non-small-cell lung cancer), KEYNOTE-006 (melanoma) and KEYNOTE-024 (non-small-cell lung cancer). The committee was aware that melanoma and non-small-cell lung cancer trials for pembrolizumab had some of the strongest evidence for a sustained response in a small number of patients. However, it recognised that the evidence suggests that treatment effect duration

varies in different types of cancers. It therefore agreed that the results from those trials were not generalisable to urothelial carcinoma.

There is no strong evidence to support the 5-year duration of treatment effect from the start of pembrolizumab treatment in the company's base case

3.15 For this review, the company used a 5-year treatment effect duration from the start of treatment with pembrolizumab in its base case, and 3 years and 10 years of treatment effect from the start of treatment in its scenario analyses. It supported its choice of a 5-year treatment effect duration in its base case by showing that the hazard ratio for overall survival for pembrolizumab compared with the UK SoC arm (using its preferred 2-stage adjustment, see section 3.5) had improved with additional follow-up data (median follow up 40.9 months, range 36.6 to 48.9 months). The comparison with the data from the original appraisal cannot be shown here as the hazard ratio is academic in confidence. The company explained that this trend was seen with the full trial population in the comparator arm of KEYNOTE-045 and when data for the UK SoC arm (unadjusted for treatment switching) was used. The company considered that a 2-year or 3-year cap on the duration of treatment effect from the start of treatment was inappropriate. This was because any longer-term benefit of pembrolizumab would not be taken into consideration, and extrapolation in the pembrolizumab arm did not fit well to the Kaplan–Meier overall survival data from the November 2018 data cut-off. The company indicated that with its preferred log-logistic curve for extrapolation of overall survival (see section 3.20), 4.5% of people having pembrolizumab were modelled to still be alive 10 years after starting treatment. Around 50% of patients in KEYNOTE-045 stopped pembrolizumab 6 months after starting treatment. The clinical expert found it plausible that 5% to 10% of people having pembrolizumab might survive to 10 years after starting treatment (with a 2-year stopping rule). A patient expert and the Cancer Drugs Fund clinical lead agreed that there

was uncertainty about how long people might survive after having pembrolizumab. This is because people with urothelial cancer tend to be older, with other comorbidities, so those people whose cancer responds to treatment could die from another cause before 10 years after starting treatment. The committee agreed that there was no strong evidence to support a 5-year or longer treatment effect, and no more than 5% of people treated with pembrolizumab might be alive after 10 years.

Based on the available evidence, a 3-year duration of treatment effect from the start of pembrolizumab is plausible

3.16 The ERG suggested that the improved hazard ratio for overall survival for pembrolizumab with the extended follow up could be explained by greater data completeness (patients in the trial progressing or dying in the longer follow-up period). The ERG preferred to use a 3-year duration of treatment effect in its exploratory base case, because it thought there was reasonably robust evidence of an effect up until 2 years from starting treatment, but limited support for an effect beyond 3 years. This was because after 3 years, there was only 1 death in the unadjusted (see section 3.5) UK SoC arm and none in the adjusted population. Although the ERG accepted that there was some evidence of sustained response for pembrolizumab, it also considered that the same was true for the UK SoC arm, with no evidence to suggest the hazard rate for long-term response was different across treatment arms after 2 years. The clinical expert advised that the sustained response from pembrolizumab was greater than that for the UK SoC arm. They stated that there was a small group of people who had pembrolizumab supporting at least a 3-year duration of treatment effect from the start of treatment. The clinical expert explained that this was not the case for people who had chemotherapy, because very few people survive beyond 2 years. The committee considered that there was robust evidence to support a 3-year treatment effect after starting pembrolizumab (2 years of treatment plus 1 year of

follow up). It concluded that, although the effect duration was uncertain, based on the available evidence a 3-year duration treatment from the start of pembrolizumab was plausible.

The company's new scenario analyses on duration of treatment effect are not appropriate for the model

3.17 In response to consultation, the company highlighted that 38.5% of people in the pembrolizumab arm had a best overall response of disease control. It presented several scenario analyses in which 38.5% of people continued to benefit from pembrolizumab for their lifetime, while the rest had the same benefit as the UK SoC arm after either 3 or 5 years. The ERG highlighted that the company had assumed the same level of response to pembrolizumab for people whose disease responded and people whose disease did not respond for the first 3 or 5 years of the model. It considered that the 2 groups would be likely to have quite different survival outcomes. The committee considered that it was arbitrary to split the pembrolizumab arm at 3 or 5 years and that a split at baseline with a different statistical analysis may have been more plausible. It also noted that the analysis was not applied to the UK SoC arm although there were people in the UK SoC arm whose disease also became stable. The committee concluded that the company's new scenario analyses were not appropriate for the model.

A 3-year to 5-year duration of treatment effect from the start of pembrolizumab treatment could be plausible

3.18 In response to consultation, the company also presented a summary of response rates from KEYNOTE-045. It highlighted that the median duration of response for responders was 29.7 months in the pembrolizumab arm and 4.4 months in the UK SoC arm. The 36-month overall survival rate was 20.7% in the pembrolizumab arm and 11.0% in the UK SoC arm, and the proportion of responses lasting 24 months or

more was 56.8% in the pembrolizumab arm and 28.3% in the UK SoC arm. The company also stated that the trial was not designed to show a treatment benefit beyond 3 years. At consultation, professional groups also highlighted these figures and stated that they were consistent with more positive long-term survival estimates than those previously assumed by the committee. The committee agreed that the Kaplan–Meier evidence did not suggest a long-term difference in hazard rates between the 2 treatment arms. It considered that there was robust evidence to support a 3-year treatment effect after starting pembrolizumab (see section 3.16). However, it also considered that the new figures suggested the relative treatment effect of pembrolizumab might continue beyond 3 years. The committee recalled that in the [NICE technology appraisal of atezolizumab](#), analyses with a treatment effect cap at 3 years after stopping were taken into account in its decision making but there was not enough evidence to support a specific duration of benefit. The committee agreed that the treatment effect duration was uncertain. It concluded that a 3-year to 5-year treatment effect from start of pembrolizumab treatment could be plausible.

The costs of pembrolizumab are likely underestimated in the model

3.19 The NHS England commissioning expert highlighted that in KEYNOTE-045, people in the pembrolizumab arm who stopped taking pembrolizumab because they had a complete response or after the 2-year stopping rule, could restart pembrolizumab for up to 1 year if their disease progressed. The company explained that 11 people out of 188 in the pembrolizumab arm had retreatment with pembrolizumab and that the costs of this were not included in the model. It explained that it was difficult to separate out the benefit these people may have had with retreatment from the overall benefit of taking pembrolizumab. The committee concluded that although only a small proportion of patients had

retreatment, the costs of pembrolizumab were likely underestimated in the model.

There are 3 plausible overall survival extrapolation curves

3.20 In its base case, the company preferred the log-logistic extrapolation for overall survival. This choice was based on statistical and visual fit to the updated overall survival data from KEYNOTE-045 (see section 3.4). The company highlighted that the log-logistic curve gave a 3.2% 5-year survival rate for the UK SoC arm, consistent with the 2% to 3% figure given by the ERG's clinical expert in the original appraisal. The ERG preferred a log-logistic curve in its exploratory base case, but also considered the log-normal and generalised gamma plausible if some patients experienced the long-term survival benefit for pembrolizumab suggested by the company (with generalised gamma being the most optimistic). If no patients experienced this long-term survival benefit, then the ERG advised that the Weibull extrapolation would be plausible. The ERG explained that the company's preferred curve and anticipated long-tailed survival profile for pembrolizumab in the long term were plausible, but unsupported by evidence (see section 3.15). The committee acknowledged that there were a number of plausible overall survival extrapolation curves. Because a small number of people having pembrolizumab may survive to 10 years after starting treatment (see section 3.15), the committee agreed that the Weibull extrapolation would penalise overall survival too harshly. But, the log-logistic, log-normal and generalised gamma were plausible if there were any survivors at 10 years. However, there was a high degree of uncertainty around long-term overall survival for pembrolizumab and all immunotherapies at 10 years because of a lack of data. So, the committee concluded that log-logistic, log-normal and generalised gamma were all plausible, and that all 3 should be taken into account in decision making.

The company's utility value estimates are appropriate

3.21 EQ-5D data were collected directly in KEYNOTE-045; these data are the preferred measure of health-related quality of life in adults. In the company's base case, vinflunine data was not included in the utility estimates because vinflunine is not used in UK clinical practice and is not included in the survival data (see sections 3.3 and 3.4). The company based the utility values on progression state and used the most recent age-related disutility algorithm. It also pooled the utility estimates across treatment arms. The committee agreed with the utility values estimates used in the company's economic model.

Cost-effectiveness estimates**The most plausible ICER for pembrolizumab compared with docetaxel and paclitaxel is likely to be over £50,000 per quality-adjusted life year gained**

3.22 The company's base-case deterministic ICER for pembrolizumab was £47,123 per quality-adjusted life year (QALY) gained compared with docetaxel or paclitaxel. This was based on the following assumptions: log-normal extrapolation for progression-free survival from 21 weeks; log-logistic extrapolation for overall survival from 24 weeks; a 5-year treatment effect duration from the start of treatment with pembrolizumab; 2-stage adjustment for treatment switching applied to the UK SoC arm. The committee noted that without the 2-stage adjustment for switching (see section 3.5) the company's ICER increased to £56,422 per QALY gained. The ERG changed the company's base case to use a Weibull extrapolation for progression-free survival from 21 weeks, which was the committee's preferred assumption (see section 3.11). This increased the ICER for pembrolizumab to £48,518 per QALY gained, and to £58,850 per QALY gained without the 2-stage adjustment for treatment switching (both ICERs including a 5-year treatment duration effect). The ERG then also included a 3-year treatment effect duration, which the committee agreed

was plausible (see section 3.18). The ICER for pembrolizumab increased to £53,678 per QALY gained with the 2-stage adjustment for treatment switching and to £65,469 per QALY gained without the 2-stage adjustment. Considering all 3 plausible options for the extrapolation of overall survival (log-logistic, log-normal and generalised gamma, see section 3.20), with the 2-stage adjustment for treatment switching, the Weibull extrapolation for progression-free survival and the 3-year treatment effect duration, the ICER ranged from £53,678 to £58,705 per QALY gained. The equivalent ICERs without the 2-stage adjustment ranged from £61,653 to £70,520 per QALY gained. The committee agreed the most plausible ICERs were somewhere between those with the 2-stage adjustment for treatment switching in the UK SoC arm, and those without the adjustment (see section 3.5). It also agreed that the ICER of £48,518 per QALY gained was at the lowest end of the range of plausible ICERs, but it was unlikely to be the most plausible because it was based on the most optimistic of the committee's preferred assumptions. When taking into account the uncertainty about the 2-stage adjustment, the uncertainty around the plausible treatment effect duration (3 to 5 years, see section 3.18) and the 3 plausible overall survival extrapolations (see section 3.20), the committee noted that the ICER could be as high as £70,520 per QALY gained. This was also unlikely to be the most plausible ICER because it was based on the most pessimistic of the committee's preferred assumptions. The committee also considered that the costs of pembrolizumab could be underestimated in the model (see section 3.19), and that increasing the costs of pembrolizumab would increase the ICERs. Considering all these factors, the committee concluded that the most plausible ICER for pembrolizumab compared with docetaxel and paclitaxel was likely to be over £50,000 per QALY gained.

End of life

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

3.23 The committee considered the advice about life-extending treatments for people with a short life expectancy in section 6.2.10 of the [guide to the methods of technology appraisal](#). 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

3.24 The median overall survival for pembrolizumab in KEYNOTE-045 using the November 2018 cut-off was 10.1 months (95% CI 7.6 to 12.9) compared with 6.2 months (95% CI 5.2 to 7.4) for UK SoC (using a 2-stage method for adjustment). The committee concluded that pembrolizumab would extend life by more than 3 months, and therefore met the end-of-life criteria.

Cancer Drugs Fund

Pembrolizumab cannot be recommended in the Cancer Drugs Fund

3.25 The aim of a Cancer Drugs Fund guidance review is to decide whether or not the drug can be recommended for routine use. Pembrolizumab for locally advanced or metastatic urothelial carcinoma in adults who have had platinum-containing chemotherapy will not remain in the Cancer Drugs Fund once the guidance review has been completed (see section 6.19 of the [guide to the processes of technology appraisal](#)).

Conclusion

Pembrolizumab is not recommended for routine use

3.26 The committee considered that the most plausible ICER was above the range that NICE normally considers to be a cost-effective use of NHS resources for a life-extending treatment at the end of life. It agreed that, given the uncertainty in the cost-effectiveness results, the most plausible ICER should be substantially below £50,000 per QALY gained (that is, the maximum weight of 1.7 applied to the normal range of maximum acceptable ICERs). Based on the range of plausible ICERs, it therefore concluded not to recommend pembrolizumab, within its marketing authorisation, for treating locally advanced or metastatic urothelial carcinoma in adults 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 Review of guidance

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

Lindsay Smith

Vice chair, appraisal committee

March 2020

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.

Amy Crossley, Kirsty Pitt

Technical leads

Nicola Hay, Lucy Beggs

Technical advisers

Kate Moore

Project manager

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