NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

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

The Department of Health and Social Care 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 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?

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 document.
- Subject to any appeal by consultees, the final appraisal document 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: 5 December 2019

Second appraisal committee meeting: TBC

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

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 NHS before this guidance was published. People having treatment outside of 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

Pembrolizumab for previously treated locally advanced or metastatic urothelial carcinoma was recommended for use in the Cancer Drugs Fund in technology appraisal 519. This appraisal reviews the evidence collected after pembrolizumab became available through the Cancer Drugs Fund.

Treatment for this indication includes docetaxel or paclitaxel. Clinical trial evidence shows that pembrolizumab significantly improves overall survival compared with docetaxel and paclitaxel.

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.

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. 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.

Because pembrolizumab has already been available through the Cancer Drugs Fund for locally advanced or metastatic urothelial carcinoma in adults who have had platinum-containing chemotherapy, it may not remain in the Cancer Drugs Fund for this indication once the guidance review has been completed.

2 Information about pembrolizumab

Pembrolizumab (Keytruda, Merck Sharp & Dohme)	
Marketing authorisation	Pembrolizumab has a marketing authorisation 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 by intravenous infusion every 3 weeks, or 400 mg by intravenous infusion every 6 weeks, until disease progression or unacceptable toxicity.
Price	£2,630 per 100 mg vial (excluding VAT; company submission). The company has a commercial arrangement (simple discount patient access scheme), which would have applied if the technology had been recommended for routine commissioning. This makes pembrolizumab available at a reduced cost. The financial terms of the agreement are commercial in confidence. 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 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 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 publication of the original appraisal of pembrolizumab. 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 guide to the processes of technology appraisal). At the time of the original appraisal of pembrolizumab for this indication, 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. Re-treatment 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 re-treatment 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 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 UK clinical practice and is the most appropriate evidence for decision making.

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

3.4 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

3.5 The November 2018 data cut from KEYNOTE-045 showed that the acceleration factor had a higher magnitude 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% confidence interval [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 wide confidence interval around the acceleration factor showed a high degree of uncertainty. The committee heard that, 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. It is not known how including these 15 patients in an adjustment would have affected the estimated incremental cost-effectiveness ratio (ICER). The ERG stated that the company had not provided an established rule for

switching. The ERG explained that the adjustment method assumed that all people switching to anti-PD-L1 or PD-1 therapy had the same overall survival benefit. Also, 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. The ERG also considered that there was potential for selection bias in relation to switching, and unmeasured prognostic factors could affect the data. The committee was concerned about the way the 2-stage adjustment was implemented in the economic model. Although the company stated that the same methodology was used in other submissions for pembrolizumab, the committee noted that the model for this appraisal appeared to incorrectly change outcomes for the pembrolizumab arm when survival for the UK SoC arm was adjusted, and these changes favoured pembrolizumab. The committee concluded that, while the ICERs using the 2-stage adjustment for treatment switching were not robust because of the apparent error in the model and the other issues above, the true overall survival benefit was probably between that seen with an adjustment for treatment switching and that without an adjustment.

Pembrolizumab is more clinically effective than docetaxel or paclitaxel

3.6 In the latest data cut of KEYNOTE-045, the median overall survival for pembrolizumab was 10.1 months (95% 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 is more clinically effective than docetaxel or paclitaxel in terms of overall survival. 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 agreed that pembrolizumab improves overall survival but does not appear to improve progression-free survival. However, because of the significant improvements in overall survival, pembrolizumab is more

clinically effective than docetaxel or paclitaxel. 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.

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 clinical effectiveness data for the PD-L1 positive subgroups 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. For the original appraisal, the company provided an indirect comparison of pembrolizumab with best supportive care, but the committee concluded that this was not useful for decision making. The company had not presented 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 in the 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 both atezolizumab and nivolumab for treating locally advanced

unresectable or metastatic urothelial cancer after platinum-containing chemotherapy, a 2-year stopping rule 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 considered 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 2-3-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 shows that the hazards cross and therefore the proportional hazards assumption does not hold. The company incorporated switching to parametric curve at week 24 in its base-case analysis because the cumulative hazard curves start 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 impact 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. In the original appraisal, the committee concluded that a lifetime treatment effect was implausible because the longest follow up was only 20.8 months. 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 impact of stopping immunotherapy at 2 years was still unknown in 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.

A 3-year duration of treatment effect from start of pembrolizumab treatment is appropriate

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 pembrolizumab compared with the UK SoC arm (using its preferred 2-stage adjustment, see section 3.4) had improved with additional follow-up data (median 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 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. 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 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. They 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 may die from another cause before reaching 10 years since starting treatment. The company indicated that with their preferred log-logistic curve for extrapolation of overall survival (see section 3.16), 4.5% of people having pembrolizumab were modelled to still be alive 10 years after starting treatment. The committee was aware that around 50% of patients in KEYNOTE-045 had stopped pembrolizumab 6 months after starting treatment. 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). However, 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. The committee recalled that in the 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 concluded that, although the treatment effect duration was uncertain, based on the available evidence a 3-year duration of treatment effect from start of pembrolizumab treatment was appropriate.

There are 3 plausible overall survival extrapolation curves

3.16 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 3.6). 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 experience the long-term survival benefit for pembrolizumab suggested by the company (with generalised gamma being the most optimistic). If no patients experience this long-term survival benefit, then the ERG advised that the Weibull extrapolation would be plausible, but that there was considerable uncertainty about long-term overall survival. The ERG explained that the company's preferred curve and anticipated long-tailed survival profile for pembrolizumab in the long term are plausible, but unsupported by evidence (see section 3.15).The committee acknowledged that there were a number of plausible overall survival extrapolation curves, and that the extrapolation of overall survival was uncertain. 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 that 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

3.17 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 3.6). 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

3.18 The company's base-case deterministic ICER was £47,123 per quality-adjusted life year (QALY) gained compared with docetaxel or paclitaxel. This was based 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 ERG made the following changes to the company's base case, which were the committee's preferred assumptions:

- a Weibull extrapolation for progression-free survival from 21 weeks (see section 3.11)
- a 3-year treatment effect duration from the start of treatment with pembrolizumab (see section 3.15).

These changes increased the ICER to £53,678 per QALY gained, which was the lowest ICER the committee considered plausible. When also considering the approach without adjustment for treatment switching, the ICER using the same ERG assumptions on progression-free survival extrapolation and treatment effect duration could be as high as £65,469 per QALY gained, when using the company's preferred overall survival extrapolation (log-logistic).

Considering all 3 plausible options for the extrapolation of overall survival (log-logistic, log-normal and generalised gamma), with the committee's other preferred assumptions, the ICER ranged from £53,678 to £58,705 per QALY gained using the company's preferred 2-stage adjustment for treatment switching. When this adjustment was removed, the ICERs then ranged from £61,653 to £70,520 per QALY gained. The committee felt the true overall survival benefit lay somewhere between that found using the 2-stage adjustment for treatment switching in the UK SoC arm, and that found without the adjustment. All plausible ICERs using the committee's preferred assumptions on treatment effect duration and progression-free survival extrapolation were above the company's preferred ICER. They were also above the level usually considered cost-effective for end-of-life treatments. This was the case when any of the 3 plausible extrapolations were used, and whether or not the 2-stage adjustment was applied.

End of life

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

3.19 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

3.20 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

3.21 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 may 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

3.22 The committee could not recommend pembrolizumab, within its marketing authorisation, for treating locally advanced or metastatic urothelial carcinoma in adults who have had platinum-containing chemotherapy. When using the committee's preferred assumptions, the ICER ranges for all 3 of the committee's preferred overall survival extrapolations were higher than would normally be considered cost-effective for end-of-life treatments, regardless of whether adjustment for treatment switching in the UK SoC arm was included (£53,678 to £58,705 per QALY gained) or excluded (£61,653 to £70,520 per QALY gained). The committee noted that these ranges of ICERs had a high degree of uncertainty associated with them. However, even if the most optimistic of the committee's preferred overall survival extrapolations was used with adjustment for treatment switching, the ICER would not be in the range usually considered cost-effective for an end-of-life treatment.

Other factors

3.23 No equality issues were identified.

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

4 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.

Lindsay Smith
Vice chair, appraisal committee
November 2019

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
Technical lead

Nicola Hay, Lucy Beggs
Technical advisers

Kate Moore
Project manager

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