NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Pembrolizumab with axitinib for untreated advanced renal cell carcinoma

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using pembrolizumab with axitinib 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: February 2020

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 with axitinib 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: 4 March 2020

Second appraisal committee meeting: TBC

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

Issue date: February 2020

1 Recommendations

1.1 Pembrolizumab with axitinib is not recommended, within its marketing authorisation, for untreated advanced renal cell carcinoma in adults.

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

Why the committee made these recommendations

Current treatment for untreated advanced renal cell carcinoma includes pazopanib, tivozanib or sunitinib. Also, cabozantinib is recommended for patients with intermediate or poor-risk cancer as defined by the International Metastatic Renal Cell Carcinoma Database Consortium. Nivolumab with ipilimumab and avelumab with axitinib cannot be comparators in this appraisal because they are not established practice. Nivolumab with ipilimumab is recommended through the Cancer Drugs Fund (and so not routinely commissioned) and avelumab with axitinib is currently being appraised by NICE.

Clinical trial evidence shows that pembrolizumab with axitinib is more effective than sunitinib for people with untreated renal cell carcinoma, but it is uncertain if there is a long-term benefit. This means the cost-effectiveness estimates are uncertain.

Uncertainties in the clinical evidence would not be resolved through data collection in the Cancer Drugs Fund. So, pembrolizumab with axitinib is not recommended for use in the fund.

Pembrolizumab with axitinib does not meet NICE's criteria to be a life-extending treatment at the end of life. The cost-effectiveness estimates are higher than what NICE normally considers an acceptable use of NHS resources. Therefore, pembrolizumab with axitinib is not recommended.

Issue date: February 2020

2 Information about pembrolizumab with axitinib

Marketing authorisation indication

2.1 Pembrolizumab (Keytruda, Merck Sharp & Dohme), in combination with axitinib (Inlyta, Pfizer), is indicated 'for the first-line treatment of advanced renal cell carcinoma (RCC) in adults'.

Dosage in the marketing authorisation

2.2 Pembrolizumab, 200 mg intravenously every 3 weeks, with axitinib, 5 mg orally twice daily.

Price

2.3 The list price of pembrolizumab is £2,630 per 100 mg vial (excluding VAT; BNF online, assessed January 2020). The cost of a single administration is £5,260. This represents approximately 3 weeks of treatment.

The company has a commercial arrangement for pembrolizumab. 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.

2.4 The list price of axitinib is £3,517 per 56 5 mg tablets (excluding VAT; BNF online, assessed January 2020). This represents approximately 28 days of treatment.

The company has a commercial arrangement for axitinib. This makes axitinib 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.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Merck Sharp & Dohme, 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 appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that:

- A time horizon of 40 years should be used to capture all relevant benefits and costs that arise from treatment for untreated metastatic renal cell carcinoma (issue 3, see technical report page 27).
- Treatment after pembrolizumab with axitinib is likely to include cabozantinib in UK clinical practice (issue 4, see technical report page 29).
- The subgroup analysis for the intermediate and poor International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk group should be informed by the constant hazard approach network meta-analysis (issue 6, see technical report page 36).

The committee recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report, table 2, page 49), and took these into account in its decision making. It discussed the following issues (issues 1, 2, 5, 7, 8, and 9), which were outstanding after the technical engagement stage.

New treatment option

People with untreated renal cell carcinoma would welcome a new treatment option

3.1 In the UK, kidney cancer is expected to cause approximately 4,500 deaths every year, with 12,600 new cases per year. Of people with kidney cancer, 80% have renal cell carcinoma. A patient expert explained that treatment with pembrolizumab with axitinib had been positive because their tumour had reduced and there were no notable side effects with the

treatment, unlike their experience with other treatment options. Patient experts confirmed that people with untreated renal cell carcinoma felt that the side effects of treatment could substantially affect quality of life. The committee recognised that for advanced renal cell carcinoma there is a high unmet need for both patients and healthcare professionals. Also, there is an unmet need for treating non-clear cell renal cell carcinoma specifically. Overall, an option that improved survival and reduced side effects would be welcomed by patients and clinicians to allow more choice of treatment and individualised care plans.

If recommended, pembrolizumab with axitinib is likely to affect eligibility for subsequent treatments

3.2 The committee considered the potential effect of pembrolizumab with axitinib on the care pathway. First-line options for treating metastatic renal cell carcinoma include tivozanib, sunitinib and pazopanib. Pazopanib is most likely to be used out of these. Cabozantinib is only recommended for patients with intermediate or poor risk. Treatment options, in particular cabozantinib, can be difficult to tolerate because of the side effects. Clinical experts expected that patients who are less fragile would be offered combination therapy instead of single agents. This is because of enhanced tolerability and a longer duration of disease control (noting that the IMDC criteria corresponds to prognosis, rather than a score of frailty). During technical engagement, clinical experts estimated that over 50% of people who had first-line treatment would have subsequent treatment. The Cancer Drugs Fund (CDF) clinical lead and the clinical experts explained that if patients have first-line treatment with pembrolizumab (a checkpoint inhibitor) plus axitinib (a tyrosine kinase inhibitor [TKI]), then they would not be eligible for nivolumab (another checkpoint inhibitor) or axitinib monotherapy later in the treatment pathway. It would be likely that subsequent treatment options would then be considered from a combination of current first-line and second-line options. The committee

concluded that the introduction of pembrolizumab with axitinib was likely to have a substantial effect on the care pathway.

Clinical evidence

The key clinical evidence came from KEYNOTE-426

3.3 The clinical evidence came from KEYNOTE-426, an open-label, randomised phase 3 trial that compared pembrolizumab plus axitinib with sunitinib (median follow up of 12.8 months). The primary outcome measures in KEYNOTE-426 were overall survival (hazard ratio 0.53; 95% confidence interval 0.38 to 0.74, p=0.00005) and progression-free survival (hazard ratio 0.69; 95% confidence interval 0.57 to 0.84, p=0.00014). Median survival was not reached in either arm. There was no evidence presented comparing pembrolizumab plus axitinib with tivozanib or pazopanib. However, tivozanib and pazopanib were assumed to have equal efficacy and safety to sunitinib. This was in line with previous appraisals:

- NICE technology appraisal on pazopanib for the first-line treatment of advanced renal cell carcinoma
- tivozanib for treating advanced renal cell carcinoma
- cabozantinib for untreated advanced renal cell carcinoma
- nivolumab with ipilimumab for untreated advanced renal cell carcinoma.

The committee concluded that pembrolizumab with axitinib was more effective than sunitinib for overall survival and progression-free survival in untreated renal cell carcinoma, but the data are immature.

A network meta-analysis was used for indirect evidence on the intermediate and poor-risk subgroup analysis

3.4 There was no direct evidence comparing pembrolizumab with axitinib with cabozantinib for the IMDC intermediate and poor-risk subgroup. The company did a network meta-analysis using data from KEYNOTE-426 and CABOSUN (a randomised phase 2 trial of cabozantinib [n=79]

compared with sunitinib [n=78]). The committee noted the small sample size of CABOSUN. Also, the network meta-analysis did not find a significant difference in progression-free survival or overall survival for the indirect comparison of pembrolizumab with axitinib and cabozantinib. Overall, the committee considered that the evidence base for the intermediate and poor-risk subgroup was weak.

Extrapolation of overall survival

There is not robust evidence to support the use of different distributions to extrapolate survival for each of the trial arms

3.5 Clinical experts expected that pembrolizumab with axitinib would offer a durable response, but they were not certain about the size of the response. They suggested that a different survival trajectory between pembrolizumab with axitinib and sunitinib could be expected. This was because of the differences in the biological mode of action between an immunotherapy and a TKI. The clinical experts explained that immunotherapy was expected to not only attack and kill the cancer cells, but also re-programme the immune system to recognise and adapt to attack and kill future cancer cells. This mode of action differed from a single TKI. The clinical experts supported an expected durable sustained response after treatment that was not expected with treatment from a single TKI. However, the NICE Decision Support Unit technical support document 14 advises that both arms should have the same extrapolation distribution unless there is substantial justification. There was theoretical justification to use different distributions for each of the trial arms. However, there is no robust evidence to support the argument that the different mode of action of the drugs would result in different survival trajectories. The committee acknowledged that the overall survival data were immature and therefore felt it was appropriate to consider various scenarios presented, including analyses when different distributions were applied. However, it concluded that there was insufficient robust evidence

to justify using different distributions to extrapolate survival for each of the trial arms.

The log-logistic distribution and the company model structure give optimistic estimates of survival

3.6 The committee considered which distribution was the most appropriate to model the overall survival for pembrolizumab with axitinib. The log-logistic distribution used had optimistic survival estimates compared with clinical estimates. The committee noted that clinical estimations might not factor in assumptions about treatment duration or a stopping rule. So, they may not be directly comparable or suitable to inform the model. The committee also examined the progression-free survival data and survival curves from KEYNOTE-426, noting that there was data for approximately 20 months of follow up. It also noted that disease had progressed in most people before 20 months, regardless of treatment. This led the committee to question both the size and length of response, and given this, whether it was valid to assume different survival trajectories for the different treatments. Overall, the committee considered the survival estimates from the log-logistic distribution used in the company base case to be optimistic.

The company economic model is likely to give optimistic survival estimates

3.7 There was an assumption in the company model that people switched to an all-cause mortality at approximately 20 years. This suggested that about 17% of people were ‘cured’. The committee asked the company whether it had examined cure fractions or if it had considered a ‘cure’ model to estimate survival. The company confirmed that cure fractions had not been considered in the economic modelling and did not intend to do a ‘mixture’ cure model. Overall the committee considered that overall survival for pembrolizumab and axitinib may have been overestimated because of having a switch to the same mortality as the general population at approximately 20 years.

The Weibull distribution gives pessimistic survival estimates

3.8 The Weibull curve was the ERG and technical team's preferred distribution for extrapolating overall survival for both pembrolizumab with axitinib and sunitinib. Clinical experts confirmed that a rising hazard rate, which was a characteristic of the chosen Weibull distribution, was not expected for people who had pembrolizumab with axitinib. Therefore, the committee agreed that the chosen Weibull distribution was likely to give pessimistic survival estimates.

There is considerable uncertainty in the survival estimates because of the immaturity of the data

3.9 The committee concluded that the most plausible survival estimates were likely to fall within the range created by the log-logistic and Weibull distribution used in the company base case and the ERG and technical team base cases respectively. It agreed to take both into account in its decision making. However, it noted that considerable uncertainty remained because of the immaturity of the evidence.

Treatment effect duration

There is not enough evidence to assume a lifetime treatment effect

3.10 The committee acknowledged that assumptions about treatment effect duration would affect expected survival. Clinical experts explained that there could be a long-term response with continued use of a TKI, but it would not be a durable response and would stop when treatment was stopped. Immunotherapy was expected to provide a durable response after stopping the treatment because of its mode of action. Although the committee thought a durable response was possible, immaturity of the data meant that this was based on clinical opinion, scientific reasoning and short-term anecdotal evidence. The committee noted that in previous NICE appraisals of checkpoint inhibitors when treatment duration was capped at 2 years, the committee:

- did not assume lifetime treatment benefit for therapy that stopped at 2 years
- examined analyses of treatment benefit waning effects that have benefit waning within 1 year and 3 years of stopping treatment (the '2+1' and '2+3' analyses in terms of time since starting treatment).

The committee therefore concluded that there was not enough evidence to assume a lifetime treatment effect and that treatment benefit waning effects should be applied in the economic model.

Because of the immaturity of data, it is appropriate to consider a 5-year waning effect scenario to estimate cost effectiveness

3.11 There was a 2-year stopping rule in the economic model for pembrolizumab. Treatment with axitinib continued until second-line treatment was indicated, for example, because of disease progression. The committee believed it was reasonable to assume some duration of response. It considered scenarios when the treatment effect stopped after 3 years, 5 years and 10 years (that is, treatment effect continued to 1 year, 3 years and 7 years after stopping pembrolizumab). The committee noted that there could be uncertainty in the economic model if treatment waning effects were applied in a scenario with continued axitinib treatment, or in scenarios when there was an implicit assumption of cure in the model. Therefore, the scenario analyses were interpreted with caution. The committee concluded that using a treatment waning effect after 5 years was appropriate given the immaturity of the data.

Application of a 2-year stopping rule

It is appropriate to apply a 2-year stopping rule for pembrolizumab

3.12 KEYNOTE-426 applied a stopping rule after 35 cycles (approximately 2 years of continuous treatment). It allowed treatment to stop and restart within the 35 cycles, and allowed for another 17 cycles of retreatment because of relapse if the patient had stopped at 35 cycles or stopped

because of complete remission. The committee noted that the follow up of 20 months was shorter than the 2-year stopping rule. So, KEYNOTE-426 did not give any information about the likely effect of the 2-year stopping rule, the proportion of patients who would restart treatment with pembrolizumab after having had 35 cycles, or the effectiveness of retreatment. It further noted that retreatment was not included in the company's economic model. The committee concluded that a 2-year treatment stopping rule in line with the clinical- and cost-effectiveness evidence was appropriate.

Health-related quality of life

The data are not appropriate for a time-to-death or a pooled health state modelling approach because of bias in the health-related quality of life data from the trial

3.13 Clinical experts confirmed that markers of disease progression, such as tumour size, may not have a strong correlation with quality of life. This suggests that a time-to-death approach to estimate health-related quality of life could be reasonable. The committee compared the utility values used for the progression-free and progressed states against those using the time-to-death approach. Utilities were calculated by progression status and differentiated by treatment. They were higher for pembrolizumab with axitinib than those calculated for sunitinib for each respective health state. The committee noted the decrement in quality of life between the progression-free and progressed states. It considered how the utility data was collected in KEYNOTE-426. Findings from all of the methods to analyse utility data may be biased and give overly optimistic estimates. This is because data collection on health-related quality of life stopped shortly after progression, leading to informative censoring bias and uncertainty in estimates for health-related quality of life at the end stages of disease. Clinical experts commented that they would expect post-progression quality of life to be influenced by subsequent-line treatments and this may be higher than estimated using the study data. Patient

experts confirmed that patients might feel the need to complete the questionnaire with more positive responses to be able to continue treatment. The committee concluded that using values from the published literature for the progressed health state would be preferable to using the trial data.

It is unclear whether an age-related decrement to health-related quality of life is appropriate because of uncertainty in overall survival estimates

3.14 The committee did not comment further on the appropriateness of including or excluding an age-related decrement to the model, because overall survival estimates were highly uncertain. However, findings from both scenarios (with and without age-related decrements) were considered in the committee's decision making.

Cost-effectiveness estimate

Because of uncertainty in the evidence, the incremental cost-effectiveness ratio (ICER) needs to be at the lower end of the acceptable range

3.15 NICE's guide to the methods of technology appraisal notes that:

- Above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER.
- When the ICER of an intervention increases in the range of £20,000 to £30,000 per QALY gained, the committee will be more cautious about recommending a technology if it is less certain about the ICERs presented.

Because of the high level of uncertainty in the clinical and economic evidence, the committee agreed that an acceptable ICER would be at the lower end of the acceptable range (that is, around £20,000 per QALY gained).

The most plausible ICER is above the acceptable range

3.16 The cost-effectiveness results are commercial in confidence and cannot be reported here. The committee considered all scenarios from the company, ERG and technical team to establish when pembrolizumab with axitinib could be considered cost effective. The committee agreed that the company base-case ICER was likely to be optimistic because of using the log-logistic distribution for extrapolation and applying a lifetime treatment effect. Also, it was above the normally acceptable range when all commercial arrangements were taken into account. This applied to both the overall renal cell carcinoma population and the intermediate and poor-risk subgroup. However, the technical team and ERG base-case ICERs were likely to be pessimistic because of using the Weibull distribution in the extrapolation of survival (see section 3.8). The committee disagreed with the company, ERG and technical t3.8eam approach of using utility values from KEYNOTE-426. It would have preferred utility values from the literature for the progression-free and progressed health states (see section 3.13). However, because of the uncertainty from the method of extrapolating overall survival, the committee did not expect that a change in utility values would affect the ICER enough for it to fall below £30,000 per QALY gained. ICERs of alternative scenarios provided by the technical team and the ERG also did not fall below £30,000 per QALY gained when all commercial arrangements were added to the analyses for either the overall renal cell carcinoma population or for the intermediate and poor-risk subgroup. The committee concluded that the most plausible ICER was within the range presented by the company base case and the technical team base case. So, the most plausible ICER was above the range normally considered as cost effective.

End of life

Pembrolizumab with axitinib does not meet the criteria to be considered as a life-extending treatment at the end of life

3.17 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal.

The committee, ERG and company agreed that pembrolizumab with axitinib does not meet end-of-life criteria for the overall renal cell carcinoma population. The committee agreed that the first end-of-life criterion (that treatment is indicated for patients with a short life expectancy, normally less than 24 months) in the intermediate and poor-risk group was not met because the median overall survival in the sunitinib arm of CHECKMATE-214 was 26 months. Estimates of overall survival for the poor-risk group could not be estimated from the economic model because it was not considered as a distinct subgroup. The committee noted that the CABOSUN trial included few poor-risk patients (15 for cabozantinib and 15 for sunitinib) and an overall survival estimate would be highly uncertain. The committee concluded there was no evidence to support that the first end-of-life criterion was met in any of the IMDC risk groups. Therefore, pembrolizumab with axitinib does not meet the criteria to be considered as a life-extending treatment at the end of life.

Cancer Drugs Fund

Pembrolizumab with axitinib does not meet the criteria to be considered for inclusion in the CDF

3.18 The committee discussed the arrangements for the CDF agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum).

Issue date: February 2020

- The modelling of overall survival data was uncertain. There was no evidence to confirm that pembrolizumab with axitinib would have a durable response and the size of response is highly uncertain. Further information could reduce this uncertainty, in particular:
  - the number of people who complete 2 years of therapy or stop because of complete remission
  - the proportion of these 2 groups that relapse and when they do
  - the response to retreatment.
- The company stated that further data cuts were expected from KEYNOTE-426. While further analysis using this data would help reduce uncertainty, the committee did not believe that the uncertainty would be resolved in the proposed timeframe with these data.
- The committee considered whether further information about progression-free survival would be useful to collect through the CDF. If everyone's disease had progressed by the end of the CDF data collection period, then it could rule out a long-term immunotherapeutic effect with pembrolizumab.
- There is no plausible potential for routine use because all plausible ICERs were above £30,000 per QALY gained when commercial arrangements were included in the analyses.

The committee concluded that pembrolizumab with axitinib did not meet the criteria to be considered for inclusion in the CDF.

Other factors

There are no equality issues relevant to the recommendations

3.19 No equality/social value judgement issues were identified.

The benefits of pembrolizumab with axitinib can be captured in the cost-effectiveness analysis

3.20 The company and clinical experts considered that pembrolizumab with axitinib was innovative. They noted pembrolizumab with axitinib had a

Issue date: February 2020

notable survival benefit and expected that the treatment would have a durable response. A clinical expert commented that, observationally, the technology seemed to have an improved adverse event profile when compared with other combination treatments. The committee agreed that while these were important potential benefits of pembrolizumab with axitinib, it had not been presented with evidence of any additional benefits that could not be captured in the measurement of QALYs.

Conclusion

Pembrolizumab with axitinib is not recommended

3.21 The committee concluded that the most plausible ICER, when commercial discounts were taken into account, was above the range that NICE normally considers to be a cost-effective use of NHS resources. It therefore concluded that pembrolizumab with axitinib is not recommended for untreated advanced renal cell carcinoma.

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.

Stephen O'Brien
Chair, appraisal committee C
January 2020

Issue date: February 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 C.

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.

Vicki Pollit
Technical lead

Caron Jones
Technical adviser

Louise Jafferally
Project manager

ISBN: [to be added at publication]

Issue date: February 2020