NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Pembrolizumab for adjuvant treatment of 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 for adjuvant treatment of renal cell carcinoma 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, sex, 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 for adjuvant treatment of renal cell carcinoma 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: 30th June 2022

Second appraisal committee meeting: 13th July 2022

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

1 Recommendations

1.1 The committee was minded not to recommend pembrolizumab for the adjuvant treatment of renal cell carcinoma at increased risk of recurrence after nephrectomy, or after nephrectomy and resection of metastatic lesions in adults.

1.2 The committee noted that pembrolizumab may be suitable for use in the Cancer Drugs Fund. Therefore the company is invited to submit a proposal for including pembrolizumab in the Cancer Drugs Fund for the adjuvant treatment of renal cell carcinoma at increased risk of recurrence after nephrectomy, or after nephrectomy and resection of metastatic lesions.

1.3 The committee recommends that NICE requests further clarification and analyses from the company to be made available for the second appraisal committee meeting, which should include:

- cost-effectiveness scenario analyses, in which the estimate of treatment effect is disease-free survival assessed by blinded independent central review and this is used in the company's base case
- scenario analyses of alternative survival extrapolations using other approaches as described in section 3.12.

Why the committee made these recommendations

Renal cell carcinoma that is at increased risk of recurrence and has been treated surgically with either a partial or radical nephrectomy is followed up with routine surveillance (regular monitoring). Pembrolizumab plus routine surveillance is a possible option as an adjuvant treatment (that is, after surgery).

Evidence from a clinical trial suggests that, after surgery, pembrolizumab plus routine surveillance increases the time people have before their cancer comes back and how long they live compared with placebo plus routine surveillance. But the

clinical trial is ongoing, so how long the treatment effects last and the risk of relapse are uncertain.

The uncertainty in the clinical evidence means that the cost-effectiveness estimates are uncertain. Also, some of the most likely cost-effectiveness estimates are higher than what NICE usually considers an acceptable use of NHS resources. Therefore, pembrolizumab is not recommended for routine use. However, pembrolizumab meets the criteria for inclusion in the Cancer Drugs Fund. So, the company is invited to present a Cancer Drugs Fund submission for consideration at the second appraisal committee meeting.

2 Information about pembrolizumab

Marketing authorisation indication

2.1 Pembrolizumab (KEYTRUDA, MSD) as 'monotherapy is indicated for the adjuvant treatment of adults with renal cell carcinoma at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The cost of a 100 mg/4 ml vial of pembrolizumab is £2,630 (excluding VAT; BNF online accessed April 2022). The cost of a 12-month course (17 cycles) of treatment is £89,420.

2.4 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.

3 Committee discussion

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

The condition

There is an unmet need for adjuvant treatments for renal cell carcinoma and people with the condition would welcome new treatment options

3.1 Renal cell carcinoma is the most common type of kidney cancer, accounting for more than 80% of cases. The highest rate is in people aged over 85 because the number of new cases increases with age. Initial treatment depends on whether, at the time of diagnosis, the cancer has spread to other parts of body (advanced renal cell carcinoma) or is localised to the kidneys. The clinical experts explained that current treatments for advanced renal cell carcinoma cause a lot of side effects. These include extreme fatigue, night sweats, rashes, chronic diarrhoea, severe mouth ulcers, nausea, hypertension, and muscle and joint pain. These can severely affect quality of life**.** For people with localised cancer, surgery is the usual treatment. There are no adjuvant treatment options available for people who have nephrectomy (partial or radical) for renal cell carcinoma at increased risk of recurrence. The patient experts explained that, after surgery, people often feel abandoned, emotionally low and anxious about the cancer returning. The clinical experts explained that adjuvant treatment options would help prevent the cancer returning and spreading, especially more aggressive and rare types. The committee noted that people with renal cell carcinoma are anxious about the cancer returning. It concluded that there is an unmet need for adjuvant treatment options, and that the addition of pembrolizumab would be welcome.

Treatment pathway and dosing regimen

The company's positioning of pembrolizumab in the treatment pathway is appropriate

3.2 The company's proposed positioning of pembrolizumab was as an adjuvant treatment after partial or complete nephrectomy in people with intermediate or high risk of recurrence. The committee found this acceptable. There is currently no globally accepted standard care for adjuvant treatment of renal cell carcinoma. Also, NICE has not appraised a medical treatment to reduce the risk of recurrence after surgery for renal cell carcinoma before. Most renal cell carcinomas are treated by complete or partial nephrectomy (see section 3.1). After tumour resection, the cancer can be graded. Risk of recurrence is greater in higher-grade cancers. Micrometastases and individual tumour cells may still be present after surgery or may occur spontaneously. They can potentially develop into larger tumours and spread to distant sites around the body. This results in advanced, unresectable tumours. The aim of adjuvant treatment is to prevent recurrence and potential progression to advanced (unresectable or metastatic) disease. The committee concluded that the positioning of pembrolizumab was acceptable for decision making.

The 400 mg dose once every 6 weeks pembrolizumab regimen is preferable

3.3 Pembrolizumab can be administered as a 200 mg dose once every 3 weeks or a 400 mg dose once every 6 weeks. The clinical experts noted that the 400 mg dosage is easier for people and reduces NHS resource use. The committee agreed that pembrolizumab can be administered at a 400 mg dose once every 6 weeks and that this would be preferable.

Clinical effectiveness

The population is narrower than that in the scope, but is aligned with the marketing authorisation and KEYNOTE-564

The clinical-effectiveness evidence presented for adjuvant pembrolizumab was from KEYNOTE-564. This was a phase 3, randomised, double-blind, placebo-controlled, multicentre clinical trial comparing pembrolizumab with placebo, both administered with routine surveillance. About 950 people were planned to be randomised 1:1 to have either placebo or pembrolizumab 200 mg, by intravenous infusion, every 3 weeks. They were adults with renal cell carcinoma that had a clear cell component. The carcinoma was study protocol-defined as being at intermediate-high or high risk of recurrence after nephrectomy, or metastasis stage M1 with no evidence of disease after nephrectomy and resection of metastatic lesions. Risk categories were based on pathological tumour node metastasis, Fuhrman grade and presence of sarcomatoid features. The intermediate-high-risk category included:

- pathological tumour stage T2, grade 4 or sarcomatoid, with no nodal involvement and no metastases
- pathological tumour stage T3, any grade, with no nodal involvement and no metastases.

The high-risk category included:

- pathological tumour stage T4, any grade, with no nodal involvement and no metastases
  any pathological tumour stage, any grade, with nodal involvement and no metastases.

The M1 stage with no evidence of disease category included people with metastatic disease who had had complete resection of primary and metastatic lesions. The population in the scope included everyone with renal cell carcinoma who had had a nephrectomy. The marketing

authorisation limits the population to people with renal cell carcinoma at increased risk of recurrence after nephrectomy, or after nephrectomy and resection of metastatic lesions. The increased risk was defined in the clinical trial as intermediate or high. The committee considered the population in the trial to be generalisable to the NHS. It queried whether a complete resection with clear margins and complete removal of metastases would be needed for the indication to use pembrolizumab. The clinical experts stated that resections are generally straightforward and that almost no one needs to have a repeat surgery. But resection of metastases will depend on factors such as the person's fitness and location of metastases. The committee concluded that the population in which the clinical-effectiveness estimates were based was narrower than that in the scope. But it agreed that it was aligned with the marketing authorisation and clinical trial.

Pembrolizumab improves disease-free survival (DFS) but the data is immature

3.4 In KEYNOTE-564, the rate of disease recurrence was lower with pembrolizumab than with placebo. The investigator-assessed (IA) hazard ratio was 0.63 (95% confidence interval [CI] 0.50 to 0.80). Median DFS and overall survival (OS) has not been reached in either treatment group of KEYNOTE-564. The immaturity of the data introduced uncertainty that may have affected the cost effectiveness (see section 3.9). The clinical experts noted that the goal of adjuvant treatment is to help people live longer. The results from KEYNOTE-564 suggested a lower risk of relapse for people who had pembrolizumab. The clinical experts noted that, in the adjuvant setting, DFS is important. This is because OS in isolation can be affected by subsequent treatments. The company agreed that the data was immature but considered that data collection beyond the planned final analysis in 2024 may not be more informative. The committee concluded that the DFS and OS data was promising but immature. It agreed that further data collection within the Cancer Drugs Fund could help to resolve some of the uncertainty.

People having treatment with pembrolizumab have more grade 3 to 5 adverse events than with placebo

3.5 The company stated that adverse events were similar between the pembrolizumab and placebo arms in KEYNOTE-564. The committee queried this. It highlighted that the results showed that people who had pembrolizumab had more grade 3 to 5 adverse events than people who had placebo. The clinical experts explained that adverse events profiles are very unpredictable and that people have differing experiences in the severity, frequency and duration of side effects. The patient experts stated that side effects can come on very quickly after pembrolizumab treatment, but agreed that people are likely to experience side effects differently. The committee recognised that active treatment will usually result in more adverse events than placebo. It noted that there were more grade 3 to 5 adverse events in the pembrolizumab group but concluded that this was because it is an active treatment.

Cost effectiveness

The company's model is structurally appropriate for decision making

3.6 The company presented a cohort-level, state-transition Markov model to estimate the cost effectiveness of pembrolizumab. The model consisted of 4 mutually exclusive health states; disease free, locoregional recurrence, distant metastases and death. The model estimated the disease pathway after nephrectomy, in that people remained disease free, had disease recurrence or died. The model's time horizon was set to 41.1 years (lifetime), Pembrolizumab treatment duration was a maximum of 17 cycles (about 1 year). The ERG considered the company's model structure to be appropriate. Also, the model structure had been accepted in a previous NICE technology appraisal guidance on pembrolizumab for adjuvant treatment of melanoma with high risk of recurrence. The committee concluded that the company's model was structurally appropriate for decision making.

Transitions from the disease-free health state are extrapolated and modelled appropriately

3.7 For transitions out of the disease-free health state the parametric models selected by the company were:

- exponential for disease free to loco regional state
- Gompertz for disease free to distant metastases state
- exponential for disease free to death state.

The company used an approach that fitted a proportional hazards parametric model to the data and applied a variable hazard ratio for pembrolizumab compared with placebo. The ERG preferred another approach that fitted independent models to both pembrolizumab and placebo groups. The committee had no preference for either approach. It stated that it would take both approaches into consideration when decision making. The committee concluded that either extrapolation approach could be justified, but noted that the extrapolations were informed by immature data and subject to uncertainty.

Whether the pattern of relapse is the same for renal cell carcinoma treated with pembrolizumab as with routine surveillance is uncertain

3.8 Pembrolizumab is given for a maximum of 17 cycles (1 year) but, in the model, the long-term DFS was extrapolated over a lifetime horizon. The aim of treatment is to remove any residual microscopic cancer after resection, and reduce the risk of relapse and progression to metastatic disease (see section 3.2). But there is substantial uncertainty around the duration of the treatment effect, the waning effect and the long-term risk of relapse. The clinical experts agreed that the pattern of relapse is unknown but the longer someone remains cancer free, the lower the risk of recurrence. The ERG considered that the risk of relapse may increase over time to match routine surveillance. It did 3 scenario analyses exploring risk of relapse for the pembrolizumab group. It modelled the transitions from 'disease free to locoregional recurrence' and from

'disease free to distant metastases' to become equal to routine surveillance at 4, 7 and 10 years. The increased risk of relapse for pembrolizumab scenarios resulted in a range in incremental cost-effectiveness ratios (ICERs) higher than what NICE considers an acceptable use of NHS resources. The company considered that there was no evidence of a treatment waning effect and that the abrupt waning at 4 years modelled by the ERG was implausible. The committee questioned at which point in the extrapolation the risk of death from background mortality exceeded the risk of relapse. The company reported that the model did not have a switch to alter risk at any point and the ERG reported that it did not explore this. The committee noted that there was a precedent of applying a waning effect in other NICE technology appraisals for immunotherapies with a treatment duration or maximum treatment time. It understood that the long-term treatment effect of pembrolizumab was uncertain even with the scenarios presented. So, it questioned whether this could be explored further in scenario analysis. The committee concluded that more scenario analyses with different treatment waning assumptions may resolve the uncertainty. It also agreed that further data collection might help resolve the uncertainty around the long-term risk of relapse.

Whether IA or blinded independent central review (BICR) assessed DFS is more methodologically robust is unclear

3.9 The primary outcome in KEYNOTE-564 was DFS assessed by an investigator. It was also assessed by BICR. The company considered that investigator assessment was more reflective of UK clinical practice and used the results of this analysis in its base case. The ERG considered the BICR assessment more methodologically robust. The company explained that the IA and BICR results for DFS were consistent. The committee noted the difference between the IA and BICR-assessed hazard ratios. The ERG noted that it would have expected the results of the IA and BICR analyses to be similar. It could not tell from the data provided what gave rise to the difference in the hazard ratios. The ERG was unable to robustly

include the BICR data in its base case, but provided an illustrative scenario of the likely effect of using BICR-assessed DFS. It applied an inflation factor to the 'disease free to locoregional' and 'disease free to distant metastases' transition probabilities using the ratio of the BICR and IA hazard ratios. This increased the ICER. The company considered investigator assessment to be reflective of clinical practice. It stated that the discrepancy between the IA and BICR-assessed results was not statistically meaningful, and could possibly have been explained by administrative processes and timings. The committee questioned why the difference in DFS estimates came about. It suggested that it could have been because the blinded independent reviewers noted fewer events with placebo and more events pembrolizumab compared with local judgements. The reason behind this was unclear. But the clinical experts noted that blinding may have been an issue for investigator assessment because the adverse events profile (see section 3.6) could have indicated who was on active treatment. The committee was uncertain about why the IA and BICR-assessed results differed. It concluded that investigator assessment reflected what is done in UK clinical practice. But it acknowledged that the BICR data was plausible and may have been more methodologically robust.

Choice of investigator or BICR assessment has a large effect on the ICERs

3.10 The committee noted that using IA or BICR results had a large effect on the ICER. The ERG considered that the BICR assessment was more robust than investigator assessment because it was unlikely to have been affected by detection bias. The committee noted it would have been helpful to have a direct comparison of IA and BICR-assessed Kaplan–Meier curves for DFS and OS. The committee concluded that there was considerable uncertainty around the investigator and BICR assessments and that this had a large effect on the cost-effectiveness estimate. It requested that the company provide further analysis to help resolve the uncertainty.

Cost-effectiveness estimates

The cost-effectiveness estimates are uncertain and include ICERs higher than what is usually consider an acceptable use of NHS resources

3.11 The committee considered the company and ERG's base cases, acknowledging the difference between survival extrapolations (see section 3.8). The committee further noted that, if BICR assessment was used, it resulted in increased ICERs (see section 3.10). 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. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee noted the high level of uncertainty, specifically whether:

- investigator or BICR assessment gives a more robust estimate of effectiveness
- the pattern of relapse is the same for renal cell carcinoma treated with pembrolizumab as with routine surveillance.

Because of confidential discounts, no ICERs can be shared. The committee considered the effect of the uncertainty on the cost-effectiveness estimates. It noted that the range of plausible ICERs included ICERs within the range usually considered by NICE to be a cost-effective use of NHS resources. But the range also included plausible ICERs that were well above what would be considered a cost-effective use of NHS resources. The committee recognised that pembrolizumab is promising in that it increased DFS, but noted the uncertainty in the cost-effectiveness estimates. Because of this, it was not persuaded that there was robust enough evidence to recommend pembrolizumab for routine commissioning. The committee concluded that pembrolizumab could not be recommended for routine use in the

NHS for the adjuvant treatment of renal cell carcinoma at increased risk of recurrence.

Cancer Drugs Fund

Pembrolizumab is a possible candidate for inclusion in the Cancer Drugs Fund

3.12 Having concluded that pembrolizumab could not be recommended for routine use in the NHS, the committee then considered whether it could be recommended within the Cancer Drugs Fund. It discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum). The committee noted that there were plausible estimates of cost effectiveness (see section 3.11. It further recognised that KEYNOTE-564 is ongoing. It agreed that admission to the Cancer Drugs fund would allow longer follow-up data to be collected. It thought that this could help resolve the uncertainty around the long-term risk of relapse and the robustness of investigator assessment compared with BICR assessment. The committee noted that pembrolizumab would meet the criteria for inclusion in the Cancer Drugs Fund. It invited a submission for the Cancer Drugs Fund from the company for consideration at the second appraisal committee meeting.

Other factors

There are no equality issues and pembrolizumab is not innovative

3.13 No equality or social value judgement issues were identified by the committee. The committee noted that there is no NICE recommended active adjuvant treatment for renal cell carcinoma post-nephrectomy at increased risk of recurrence. But, when focusing specifically on relevant benefits associated with innovation, the committee considered that there were no additional benefits that had not been captured in the QALY.

Conclusion

There is not enough evidence to recommend pembrolizumab for routine commissioning but inclusion in the Cancer Drugs Fund needs exploring

3.14 The committee would like to see a proposal for the Cancer Drug Fund. It recognised that pembrolizumab is promising in that it increased DFS. It also considered that the approaches chosen by the company and the ERG to extrapolate and model transitions from the disease-free health state were both reasonable. But the committee considered that the immature data meant it was uncertain whether the pattern of relapse was the same for renal cell carcinoma treated with pembrolizumab as with routine surveillance over time. Also, the committee recognised there was uncertainty around whether the IA analysis or the BICR analysis provided a more robust estimate of treatment effect. The committee noted that these uncertainties resulted in a plausible ICER range that included ICERs higher than what NICE usually considers an acceptable use of NHS resources. So, it could not recommend pembrolizumab for routine use in the NHS. The committee concluded that pembrolizumab would meet the criteria needed to be considered for inclusion in the Cancer Drugs Fund. It invited a submission for the Cancer Drugs Fund from the company for consideration at the second appraisal committee meeting.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review 3 years after publication of the guidance. This will allow KEYNOTE-564 to be completed and the final results for disease-free and overall survival to be reported. NICE welcomes comment on this proposed date. NICE will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Dr Charles Crawley
Chair, appraisal committee
May 2022

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 B.

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.

Susan O'Connell, Megan Dale
Technical lead

Rufaro Kausi
Technical adviser

Rumana Zaman, Jeremy Powell
Project managers

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