NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Pembrolizumab for adjuvant treatment of renal cell carcinoma

1 Recommendations

1.1 Pembrolizumab is recommended, within its marketing authorisation, as an option for the adjuvant treatment of renal cell carcinoma at increased risk of recurrence after nephrectomy, with or without metastatic lesion resection, in adults. It is recommended only if the company provides it according to the commercial arrangement.

Why the committee made these recommendations

People who have had renal cell carcinoma that has been treated surgically with either a partial or radical nephrectomy, and that is at increased risk of recurrence, have routine surveillance (regular monitoring) as follow-up. 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.

The cost-effectiveness estimates for pembrolizumab as adjuvant treatment are within the range that NICE normally considers an acceptable use of NHS resources. So, it is recommended.

2 Information about pembrolizumab

Marketing authorisation indication

2.1 Pembrolizumab (Keytruda, Merck Sharp and Dohme) 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 per 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. 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 and Dohme (MSD), a review of this submission by the external 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 (after surgery) 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 renal cell carcinoma at increased 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. After tumour resection, the cancer can be graded. Risk of recurrence is greater in higher-grade cancers. After surgery, micrometastases and individual tumour cells may still be present or may reoccur. 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, and they would prefer to use pembrolizumab every 6 weeks. The committee agreed that pembrolizumab is likely to be administered at a 400 mg dose once every 6 weeks, and that this would be preferable to a 3-weekly dosage.

Clinical effectiveness

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

3.4 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 study protocol defined increased risk as being carcinoma 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, or grade 4, sarcomatoid or both, 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

3.5 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. 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, although the data was immature, people who had pembrolizumab had a lower risk of relapse than people who did not.

Grade 3 to 5 adverse events are more common with pembrolizumab than with placebo

3.6 The company stated that adverse events were similar between the pembrolizumab and placebo treatment groups 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 than placebo group. But it concluded that this would be expected with an active immunotherapy.

Cost effectiveness

The company's model is structurally appropriate for decision making

3.7 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 completely resected stage 3 melanoma. 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

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

- Approach 1: standard parametric models fitted independently to pembrolizumab and placebo data from KEYNOTE-564.
- Approach 2: standard proportional hazards (PH) parametric models (exponential, Weibull and Gompertz) jointly fitted to pembrolizumab and

placebo data from KEYNOTE-564, with a time-constant hazard ratio applied for pembrolizumab compared with placebo (PH model).

- Approach 3: standard PH parametric models (exponential, Weibull and Gompertz) jointly fitted to pembrolizumab and placebo data from KEYNOTE-564, with a hazard ratio for pembrolizumab compared with placebo applied to year 1 and another hazard ratio applied for year 2 onwards (time-varying PH model).

The company preferred approach 3. The ERG considered that, when patient level data is available from a trial, using PH modelling is not necessary. It considered that independent models for each treatment group were preferred, as in NICE's Decision Support Unit Technical Support Document 14. So, the ERG considered approach 1 to be a more robust method for extrapolating the cause-specific time-to-event data used in the model. The committee concluded that either extrapolation approach could be justified but preferred approach 1.

Choice of extrapolation approach affects the ICERs in all cost-effectiveness scenarios

3.9 Incremental cost-effectiveness ratios (ICERs) were calculated using the ERG's preferred approach 1 (see section 3.8) with treatment waning scenarios (see section 3.10) and scenarios comparing investigator assessment or blinded central independent review (BICR; see section 3.11). This resulted in ICERs that included some which were higher than what NICE usually considers an acceptable use of NHS resources. The committee concluded that the ERG's approach was preferred for extrapolation, noting that it aligned with NICE's Decision Support Unit Technical Support Document 14.

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

3.10 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). There is substantial uncertainty around the duration of the treatment effect, the waning of the treatment 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. It also applied treatment waning effects to 100%, 50% and 20% of people. The company considered treatment waning to be implausible in the adjuvant setting. The company presented scenarios exploring the assumptions that at 7 or 10 years, either 15% or 20% of people in the pembrolizumab treatment group would experience risk of relapse equal to routine surveillance. The clinical experts agreed that most relapses occur within 5 years and the risk at 10 years is much smaller. The committee understood that the long-term treatment effect of pembrolizumab was uncertain even with the scenarios presented. It concluded that a treatment waning effect should have been considered, and took account of the scenarios explored by the ERG and the company in its decision making.

Whether IA or BICR is a better estimate of DFS is uncertain

3.11 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, but the clinical expert noted that they would expect to see differences in the IA and BICR results. The committee agreed that investigator assessment reflected what is done in UK clinical practice. It concluded that it would consider the cost-effectiveness estimates using both approaches. But it thought that the BICR data was more methodologically robust and provided a plausible estimate of DFS.

Cost-effectiveness estimates

Pembrolizumab is recommended for routine use in the NHS

3.12 The committee acknowledged the difference between survival extrapolations in the company's and ERG's base cases (see section 3.8). It also 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 uncertainty about whether investigator assessment or BICR gives a more robust estimate of DFS. But it expressed a preference for BICR analysis. It considered both the company's and ERG's preferred assumptions and concluded that its preferred assumptions were:

- approach 1, that is, the standard parametric models fitted independently to pembrolizumab and placebo data from KEYNOTE-564 to extrapolate the cause-specific time-to-event data used in the model
- cost-effectiveness estimates using both the IA DFS and the BICR-assessed DFS
- including treatment waning in the pembrolizumab treatment group.

The committee considered what effect the uncertainty around the approach used to extrapolate DFS data had on the cost-effectiveness estimates. It recognised that pembrolizumab is promising in that it increased DFS. It also noted that the range of plausible ICERs using its preferred assumptions and with the confidential discount applied were in the range usually considered a cost-effective use of NHS resources. The committee concluded that pembrolizumab could be recommended for routine use in the NHS for the adjuvant treatment of renal cell carcinoma at increased risk of recurrence.

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.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has renal cell carcinoma and the doctor responsible for their care thinks that pembrolizumab is the right treatment, it should be available for use, in line with NICE's recommendations.

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.

Chair

Dr Charles Crawley
Chair

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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