NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Pembrolizumab for untreated metastatic or unresectable recurrent squamous cell head and neck cancer

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 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: January 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 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 February 2020

Second appraisal committee meeting: TBC

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

1 Recommendations

1.1 The committee is minded not to recommend pembrolizumab as an option for untreated metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a combined positive score (CPS) of 1 or more.

1.2 The committee recommends that NICE requests further clarification and analyses from the company, which should be made available for the next appraisal meeting. These should include the following for pembrolizumab monotherapy and pembrolizumab with platinum chemotherapy and 5-fluorouracil (5-FU):

- Provide a full comparison of baseline patient characteristics for the 2 subgroups: people whose cancer started inside or outside the oral cavity. Highlight any imbalances in the baseline patient characteristics in each of the subgroups (see section 3.6).
- Provide overall survival data (Kaplan–Meier curves, hazard ratios) for the 2 subgroups. Carry out formal statistical analysis to adjust for imbalances in baseline patient characteristics in the subgroups (see section 3.6). Justify which adjustment method was used and do not restrict it to just the covariates that are unbalanced (see NICE DSU technical support document 17).
- Provide overall survival extrapolation curves, after adjusting for imbalances in baseline patient characteristics for the 2 subgroups (see section 3.10), and justify the choice of distribution curve used.
- Provide an alternative utility value for progressed disease. This should come from published literature (see section 3.11).
- Explore techniques to provide full incremental analyses for the 2 subgroups. The incremental analysis should incorporate all of the above, a 2-year stopping rule (see section 3.8), and a 5-year duration of treatment effect (see section 3.9). In addition, carry out alternative analyses using the company's fractional polynomial network meta-

analysis and the evidence review group's approach of using data from KEYNOTE 048 for the comparison of pembrolizumab with platinum chemotherapy and 5-FU (see section 3.7).

Why the committee made these recommendations

Treatment of metastatic or unresectable recurrent HNSCC depends on where it started. If it starts inside the oral cavity (mouth), it's usually first treated with cetuximab, platinum chemotherapy and 5-FU. If it starts outside the oral cavity it's treated with platinum chemotherapy and 5-FU.

Clinical trial evidence shows that people who have a type of metastatic or unresectable recurrent HNSCC defined as PD-L1 positive with a CPS of 1 or more live longer if they have pembrolizumab (on its own or with other chemotherapy drugs) than if they have cetuximab with platinum chemotherapy and 5-FU. But there's uncertainty over the evidence because the comparator drugs in the trial do not reflect what happens in the NHS in England. In the comparator arm of the trial all people were given cetuximab with platinum chemotherapy and 5-FU, regardless of whether the cancer started inside or outside the oral cavity. This is not established clinical practice in the NHS in England. Separate clinical evidence for people whose cancer started outside the oral cavity was not provided. Also, information about the clinical and cost effectiveness for the 2 different patient groups (cancer starting inside or outside the oral cavity) was incomplete. Therefore, NICE is unable to make a recommendation about pembrolizumab and has asked for more clinical and cost-effectiveness evidence.

2 Information about pembrolizumab (monotherapy or in combination)

Marketing authorisation indication

2.1 Pembrolizumab (Keytruda, Merck Sharp & Dohme) has a UK marketing authorisation as monotherapy or with platinum and 5-fluorouracil (5-FU) chemotherapy '…for the first-line treatment of metastatic or unresectable

recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a CPS [combined positive score] ≥ 1'.

Dosage in the marketing authorisation

2.2 Pembrolizumab monotherapy consists of 200 mg taken by intravenous infusion every 3 weeks, or 400 mg every 6 weeks, until disease progression or unacceptable toxicity.

2.3 Pembrolizumab in combination with platinum chemotherapy and 5-FU consists of 200 mg taken by intravenous infusion every 3 weeks until disease progression or unacceptable toxicity.

2.4 PD-L1 mutation status should be determined using a validated test.

Price

2.5 Pembrolizumab costs £2,630 for a 100 mg vial, excluding VAT (BNF online, accessed December 2019).

2.6 The company has a commercial arrangement (managed access agreement including a commercial access agreement). 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 (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 2 issues were resolved during the technical engagement stage, and agreed that:

- A 2-year stopping rule for pembrolizumab is appropriate for decision making (table 3, page 52 of the technical report).
- Pembrolizumab (monotherapy and in combination) meets the end-of-life criteria for the whole PD-L1 with combined positive score (CPS) of 1 or more population in KEYNOTE-048 (table 3, page 52 of the technical report). However, the committee had concerns about whether it meets the end-of-life criteria for the 2 subgroups: people whose cancer started inside or outside the oral cavity (see section 3.14).

It recognised that there were remaining areas of uncertainty associated with the analyses presented (table 2, pages 50 and 51 of the technical report), and took these into account in its decision making. It discussed the following issues, which were outstanding after the technical engagement stage.

Clinical need

A new treatment option is needed for people with recurrent or metastatic HNSCC

3.1 The patient experts' submission stated that metastatic or unresectable recurrent squamous cell head and neck cancer (HNSCC) has a big impact on the people living with the disease and their carers and family. Having a complete response to treatment or being progression free for as long as possible, as well as better quality of life, is important to people. The clinical experts explained that this condition can be debilitating, with distressing symptoms such as a sore mouth, finding it hard to swallow or eat, loss of appetite and weight loss. They also said that many people have major surgery, which can change their appearance and have a psychological and social impact on their life. The clinical experts said that pembrolizumab's benefit is that it is better tolerated than existing treatments, with fewer of the side effects seen with cetuximab such as

rash, diarrhoea and low magnesium. The committee concluded that there is a clinical need for an effective treatment that improves quality of life.

The decision to use pembrolizumab monotherapy or combination therapy is made on a case-by-case basis

3.2 The marketing authorisation for pembrolizumab is as a monotherapy or in combination with platinum chemotherapy and 5-fluorouracil (5-FU). The clinical experts explained that combination therapy is usually offered to people with a high disease burden, or whose disease is progressing rapidly or has relapsed after chemotherapy. They also explained that monotherapy is offered to people with a low disease burden, with disease progressing at the expected rate, or to people who are not able to tolerate combination therapy. The summary of product characteristics also states that 'the risk of adverse reactions with combination therapy relative to pembrolizumab monotherapy should be considered and the benefit/risk ratio of the combined therapy evaluated on an individual basis'. The committee accepted that the decision about whether someone is offered monotherapy or combination is on a case-by-case basis. Several clinical factors are taken into account and, although some factors apply to both groups, such as good performance status, there are differences, for example in disease burden and speed of disease progression. The committee concluded that, because the decision about whether someone is offered monotherapy or combination is made on a case-by-case basis, it is not possible to clearly define different distinct patient populations who would be offered one treatment over the other.

The comparators are cetuximab with platinum chemotherapy and 5-FU for cancer inside the oral cavity and platinum chemotherapy and 5-FU for cancer outside the oral cavity

3.3 The clinical experts explained that people with metastatic or unresectable recurrent HNSCC receive either cetuximab with platinum chemotherapy and 5-FU or platinum chemotherapy and 5-FU. People whose cancer started inside the oral cavity are offered cetuximab with platinum

chemotherapy and 5-FU in line with NICE's technology appraisal guidance on cetuximab for HNSCC. However, the committee heard that some people whose cancer started in the oral cavity may not be considered fit enough to have cetuximab with platinum chemotherapy and 5-FU because of toxicity. They're offered platinum chemotherapy and 5-FU only. People whose cancer started outside the oral cavity are offered platinum chemotherapy and 5-FU. After cetuximab with platinum and 5-FU chemotherapy or platinum and 5-FU chemotherapy people may be offered either further platinum-based chemotherapy, or nivolumab through the Cancer Drugs Fund (see NICE's technology appraisal guidance on nivolumab for HNSCC). People who are not well enough to have further treatment are offered best supportive care. The committee noted that the marketing authorisation for pembrolizumab monotherapy or with cetuximab and platinum chemotherapy and 5-FU was as a first-line treatment for recurrent or metastatic HNSCC but did not specify tumour location. The committee agreed that cetuximab with platinum and 5-FU chemotherapy was the relevant comparator for pembrolizumab for people whose cancer started inside the oral cavity. This is because most people offered pembrolizumab are likely to have similar patient characteristics to people offered the cetuximab combination, such as a good performance status. The committee also agreed that platinum chemotherapy and 5-FU was the relevant comparator for pembrolizumab for people whose cancer started outside the oral cavity.

Clinical evidence

People with PD-L1 positive CPS 1 or more HNSCC who have pembrolizumab live longer than people who have cetuximab with platinum chemotherapy and 5-FU

3.4 The clinical evidence for pembrolizumab came from the ongoing KEYNOTE-048 randomised controlled trial. People in the trial had recurrent or metastatic HNSCC and were randomised to receive pembrolizumab monotherapy (n=301), pembrolizumab with platinum

chemotherapy and 5-FU (n=281) or cetuximab with platinum chemotherapy and 5-FU (n=300). After disease progression people were able to have further treatment, including the anti-PD-L1 drug nivolumab. The population in the marketing authorisation is adults whose tumours express PD-L1 with a CPS of 1 or more. This was based on a prespecified subgroup analysis of KEYNOTE-048. Because nivolumab is only available in the NHS through the Cancer Drugs Fund it cannot be considered as a comparator in the appraisal. So, the company adjusted the overall survival data to account for this by using the simplified 2-stage method. Analysis of KEYNOTE-048 data showed that pembrolizumab (monotherapy and in combination) extended overall survival compared with cetuximab with platinum chemotherapy and 5-FU for the PD-L1 CPS 1 or more subgroup population with recurrent or metastatic HNSCC. This produced a hazard ratio of 0.71 (95% confidence interval [CI]: 0.57 to 0.89; p=0.0027) for pembrolizumab monotherapy and 0.62 (95% CI: 0.50 to 0.78; p<0.0001) for pembrolizumab with platinum chemotherapy and 5-FU. The committee noted that the results showed a statistically significant difference in overall survival at 18 months and concluded that pembrolizumab (monotherapy or in combination) compared with cetuximab with platinum chemotherapy and 5-FU improved overall survival in the PD-L1 CPS 1 or more subgroup of KEYNOTE-048.

The KEYNOTE-48 clinical trial is not wholly applicable to clinical practice in England

3.5 People included in KEYNOTE-48 had an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1. They may be in better health than people with recurrent or metastatic HNSCC in the NHS. In the comparator arm of KEYNOTE-048, only 31% of people had cancer that started in the oral cavity. The 69% of people whose cancer had started outside the oral cavity had treatment that is not standard care in the NHS: cetuximab with platinum and 5-FU. In the NHS in England, these people are offered platinum chemotherapy and 5-FU (see section 3.3). The committee agreed that it was not clear what effect this would have on the

relative effectiveness of pembrolizumab monotherapy or combination therapy in the whole PD-L1 CPS 1 or more population in the trial. The committee recognised that KEYNOTE-048 was a well-conducted trial and was the best available evidence for pembrolizumab. But it concluded that the results of the trial may not be generalisable to clinical practice because the trial was not wholly applicable to current clinical practice in England.

Pembrolizumab's clinical effectiveness in cancer starting inside the oral cavity and in cancer starting outside is unclear

3.6 The committee agreed that, because current treatment options are different for cancer that started inside or outside the oral cavity in the NHS in England (see section 3.3), it was appropriate to consider the clinical effectiveness of pembrolizumab in the 2 population subgroups: cancer starting inside or outside the oral cavity. The company had provided overall survival results from KEYNOTE-048 for the subgroup of people whose cancer started inside the oral cavity (these results are confidential and therefore cannot be reported here). The committee heard from the company that the analysis of this subgroup should be viewed with caution because it was a post-hoc analysis not powered to show a difference between treatments. The committee noted that the company had provided the baseline characteristics in this subgroup. The committee heard that there were imbalances in the prognostic baseline characteristics of the people in this subgroup. The committee also heard from the company that it did not look at the prognostic baseline characteristics of the people in the subgroup of people whose cancer started outside the oral cavity. The committee recognised that the analyses for these subgroups are uncertain because they were not prespecified and therefore not powered for such analyses. However, the committee concluded that it would like to see clinical effectiveness analyses for the 2 subgroups of people: those whose cancer started inside the oral cavity and outside, taking into account any imbalances in the baseline patient characteristics in each of the subgroups.

Indirect treatment comparisons

The most appropriate analysis for comparing pembrolizumab with platinum chemotherapy and 5-FU is not certain

3.7 The company did a fractional polynomial network meta-analysis to compare pembrolizumab (monotherapy and in combination) with platinum chemotherapy and 5-FU. This was done because there was no direct evidence comparing pembrolizumab (monotherapy and in combination) with platinum chemotherapy and 5-FU. The committee heard from the company that this type of analysis best accounted for any study-observed differences. The ERG explained that it was concerned about the analysis's validity because the company did not consider the plausibility of the hazard ratios estimated by the fractional polynomial model. The company did not say how the 2 categories of fractional polynomial models were assessed. The ERG was also concerned that the populations in the trials included in the meta-analysis were different from those in KEYNOTE-048. For example, the trials were not restricted to people with PD-L1 CPS 1 or more status, as in KEYNOTE-48, which was likely to introduce heterogeneity. In addition, the ERG was concerned that the meta-analysis was not stratified by where the cancer started. It preferred to use Kaplan–Meier data from the cetuximab with platinum chemotherapy and 5-FU arm of KEYNOTE-048 to represent people whose cancer started outside the oral cavity. The ERG said that this method was simple, transparent and based on data from a high-quality trial. The clinical experts agreed that the ERG approach was reasonable because, in the trial that supported the use of cetuximab with platinum chemotherapy and 5-FU for head and neck cancer (the EXTREME trial). The trial showed a benefit with cetuximab with platinum chemotherapy and 5-FU only in cancers that started inside the oral cavity when compared with platinum chemotherapy and 5-FU. The results from the company's fractional polynomial network meta-analysis and the ERG's approach are considered academic in confidence and therefore cannot be reported here. The committee noted the results from the 2 approaches

and considered that the company's approach may overestimate the effectiveness of pembrolizumab (monotherapy and in combination), while the ERG's approach may overestimate the effectiveness of platinum and 5-FU chemotherapy. The committee agreed that both approaches were subject to uncertainty and, given the differing results from the 2 approaches, the true treatment effect of pembrolizumab (monotherapy and in combination) compared with platinum chemotherapy and 5-FU was uncertain. The committee concluded that it would take both approaches into account in its decision making.

The company's modelling approach is appropriate for decision making

3.8 The company presented a 3-state partitioned survival model (progression free, progressed disease and death) comparing pembrolizumab (monotherapy or in combination) with cetuximab with platinum chemotherapy and 5-FU. The company included a 2-year treatment stopping rule in the model. The summary of product characteristics for pembrolizumab states that treatment should continue until disease progression or unacceptable toxicity. Implementing a 2-year stopping rule is consistent with NICE's technology appraisal guidance on pembrolizumab for other indications. The clinical experts also considered that a 2-year stopping rule was appropriate for pembrolizumab in this appraisal. The committee concluded that the modelling approach was appropriate for decision making.

A 5-year treatment benefit for pembrolizumab is appropriate

3.9 The company used a time horizon of 20 years to capture all relevant costs and benefits for people having treatment. The company assumed a treatment benefit for pembrolizumab (monotherapy or in combination) for the full 20 years from starting treatment. The committee agreed with the ERG and clinical experts that this assumption was optimistic. The ERG's preferred analyses used treatment effect over 5 years (that is, applying a hazard ratio of 1 to both the pembrolizumab and cetuximab with platinum and 5-FU arms 5 years after starting treatment, which is 3 years after

stopping treatment) because in NICE's technology appraisal guidance for nivolumab for recurrent or metastatic HNSCC the preferred duration of treatment effect was 5 years. The clinical experts said that conceptually it was possible that pembrolizumab's treatment effect could last as long as 10 years because immunotherapies such as pembrolizumab have a different mechanism to cytotoxic therapies. Once antitumour immunotherapy occurs, it is plausible that the effect of treatment could be maintained. But the clinical experts highlighted that this was only speculative because there was not much long-term data for pembrolizumab from KEYNOTE-048. The clinical expert said that the treatment effect duration for pembrolizumab could not be transferred from one disease area to another because of differences in the physiology and genetic profile of the tumours. The committee agreed that, although it was biologically plausible for the treatment effect to continue after stopping pembrolizumab, its duration was uncertain. The committee concluded that a 20-year duration of treatment benefit for pembrolizumab (monotherapy and in combination) was not supported by the evidence, therefore the ERG's analyses using a 5-year duration were more appropriate and consistent with the previous head and neck cancer immunotherapy appraisal.

Overall survival should be modelled for the 2 subgroups: cancer starting inside the oral cavity or outside

3.10 To estimate overall survival in KEYNOTE-048 the company used a piecewise log-logistic extrapolation of the Kaplan–Meier curve from KEYNOTE-048 for pembrolizumab monotherapy and a log-normal for pembrolizumab combination therapy. This estimated the mean overall survival to be 12.72 months with pembrolizumab monotherapy, and 14.28 months with pembrolizumab combination therapy, assuming a 20-year time horizon in the model. The ERG highlighted that using log-logistic and log-normal distributions results in implausible survival estimates because of the long tails associated with them (that is, a small number of people live for a long period of time). It explained that its

preferred distribution was Weibull as this gave the most clinically plausible results. The clinical experts said that the company's and ERG's preferred survival estimates were both plausible for cetuximab with platinum chemotherapy and 5-FU and platinum chemotherapy and 5-FU treatments. But they considered that the ERG's survival estimates for pembrolizumab (monotherapy and in combination) were the most plausible. The company's and the ERG's extrapolation of overall survival was for the PD-L1 CPS 1 or more subgroup of KEYNOTE-048. Separate analysis of the populations whose cancer started inside or outside the oral cavity was not provided. The committee concluded that it would like to see overall survival modelled, adjusted for imbalances in the baseline patient characteristics, for the 2 subgroups: people whose cancer started inside or outside the oral cavity.

A lower utility value for progressed disease should be used, sourced from published literature

3.11 The company used a health-related quality of life utility value of 0.71 in its base case for people with progressed metastatic disease. Based on the description of the health states in the model, the clinical experts said that this was high for people who are normally in very poor health and therefore may be overestimated. The committee noted that health-related quality of life was measured in the trial 30 days after progression, so there was a possibility of informative censoring (that is, participants in the trial are lost to follow-up because of reasons related to the study design). The committee agreed that the utility value for progressed disease used in the company's model was too high. The committee concluded that it would like to see cost-effectiveness analyses using a lower utility value for progressed disease than used in the company's base case and that it should be sourced from published literature.

Cost-effectiveness results

The company's cost-effectiveness results are not appropriate for decision making

3.12 The company's base-case pairwise analyses based on the whole trial population (PD-L1 CPS 1 or more):

- assumed a 20-year duration of treatment effect (see section 3.9)
- used a log-logistic distribution curve for pembrolizumab monotherapy to model overall survival (see section 3.10)
- used a log-normal distribution curve for combination therapy to model overall survival (see section 3.10)
- used clinical data from the company's fractional polynomial network meta-analysis for the comparison of pembrolizumab with platinum chemotherapy and 5-FU (see section 3.7).

All cost-effectiveness analyses included the company's commercial arrangement for pembrolizumab. Pairwise analyses showed that pembrolizumab monotherapy dominated (was more effective and cheaper than) cetuximab with platinum chemotherapy and 5-FU. The incremental cost-effectiveness ratio (ICER) for pembrolizumab combination therapy compared with cetuximab with platinum chemotherapy and 5-FU was £9,255 per quality-adjusted life year (QALY) gained. Using the fractional polynomial network meta-analysis to estimate overall survival, compared with platinum chemotherapy and 5-FU, the ICERs per QALY gained were:

- £31,070 for pembrolizumab monotherapy
- £31,212 for pembrolizumab combination therapy.

When the confidential commercial arrangement for cetuximab was taken into account, the ICERs for pembrolizumab monotherapy and combination therapy increased (the ICERs are confidential and therefore cannot be reported here). The committee noted that the company's base-case ICERs did not include its preferred assumptions:

- analyses based on baseline characteristics of the 2 subgroups and where the cancer started (see sections 3.6 and 3.10)
- treatment duration of 5 years (see section 3.9)
- a lower utility value for progressed disease (see section 3.11)
- a fully incremental analysis (a combined single analysis in which cetuximab with platinum chemotherapy and 5-FU, or platinum chemotherapy and 5-FU, is compared with pembrolizumab monotherapy, which in turn is then compared with pembrolizumab in combination) because the populations who would be offered one treatment over the other are not distinct patient populations (see section 3.3).

The committee therefore concluded that the company's cost-effectiveness analyses were not appropriate for its decision making and agreed not to consider them further.

The ERG's preferred exploratory cost-effectiveness analyses are not appropriate for decision making

3.13 The ERG presented cost-effectiveness analyses (pairwise and fully incremental) for pembrolizumab (monotherapy or in combination) compared with cetuximab with platinum chemotherapy and 5-FU, and compared with platinum chemotherapy and 5-FU for the 2 population subgroups (people whose cancer started inside or outside the oral cavity). The ERG's analyses:

- assumed a 5-year duration of treatment effect (see section 3.9)
- used a Weibull distribution curve for modelling overall survival for pembrolizumab monotherapy and pembrolizumab combination therapy (see section 3.10)
- used Kaplan–Meier data from the cetuximab with platinum chemotherapy and 5-FU chemotherapy arm of KEYNOTE-048 for the comparison of pembrolizumab with platinum chemotherapy and 5-FU

for people whose cancer started outside the oral cavity (see section 3.7).

All cost-effectiveness analyses included the company's commercial arrangement for pembrolizumab.

For people whose cancer started inside the oral cavity, pairwise analyses showed that pembrolizumab monotherapy dominated cetuximab with platinum chemotherapy and 5-FU. The ICER for pembrolizumab combination therapy was £16,553 per QALY gained compared with cetuximab with platinum chemotherapy and 5-FU.

For people whose cancer started outside the oral cavity, the pairwise ICERs per QALY gained compared with platinum chemotherapy and 5-FU were:

- £56,085 for pembrolizumab monotherapy
- £67,386 for pembrolizumab combination therapy.

The ICERs per QALY gained for the fully incremental analysis using the ERG's preferred analyses for people whose cancer started outside the oral cavity were:

- £56,052 for pembrolizumab monotherapy compared with platinum chemotherapy and 5-FU
- £114,224 for pembrolizumab combination therapy compared with pembrolizumab monotherapy.

For people whose cancer started inside the oral cavity, the ERG provided a fully incremental analysis including the confidential commercial arrangement for cetuximab. The ICERs were below £50,000 for pembrolizumab monotherapy compared with cetuximab with platinum chemotherapy and 5-FU and pembrolizumab combination therapy compared with pembrolizumab monotherapy (the ICERs are confidential and therefore cannot be reported here). The ERG considered the fully

incremental analysis to be the most appropriate analysis because there are 2 interventions being appraised for the same population: pembrolizumab monotherapy and in combination. The committee agreed that the ERG's fully incremental analysis was its preferred analysis. This was because it took into account that 2 interventions were being appraised (pembrolizumab monotherapy and pembrolizumab in combination) and that the populations who would be offered one treatment over the other are not distinct patient populations (see section 3.3). For the 2 subgroups (cancer starting inside the oral cavity or outside) the ERG used data from KEYNOTE-048. The committee recalled that it was unclear whether these subgroups were balanced for patient baseline characteristics (see sections 3.6 and 3.10). It also noted that these analyses did not include a lower utility value for progressed disease (see section 3.11). Because neither of these were addressed in the ERG's cost-effectiveness analyses, the committee agreed that the ERG's cost-effectiveness analyses were not appropriate for its decision making. The committee concluded that it would like to see fully incremental cost-effectiveness analyses for the 2 subgroups, using survival data that had been adjusted for any imbalances in baseline patient characteristics in each of the subgroups and a lower utility value for progressed disease than used in the company's base case.

End of life

Analysis of the 2 subgroups (cancer starting inside or outside the oral cavity) is needed to decide on extension to life

3.14 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. Evidence for the whole trial population from KEYNOTE-048 showed that the median overall survival for people having cetuximab with platinum chemotherapy and 5-FU was 10.3 months (95% CI: 9.0 to 11.5). The committee accepted that, based on the whole trial population, pembrolizumab (monotherapy and in combination) meets the

short life expectancy criterion for end of life. It also noted that the company's economic model suggested that pembrolizumab (monotherapy and in combination) provided an extension to life of more than 3 months (12.72 months with pembrolizumab monotherapy, and 14.28 months with pembrolizumab combination therapy). Based on the modelled estimates the committee accepted that, for the whole trial population, pembrolizumab (monotherapy and in combination) extended life by more than 3 months. However the committee recalled that it would like to see all clinical data by primary tumour location subgroup (see section 3.6) and therefore concluded that clinical effectiveness evidence in the subgroup of people whose cancer started inside the oral cavity and in the subgroup of people whose cancer started outside the oral cavity is needed to inform a decision on whether pembrolizumab (monotherapy or in combination) meets the extension to life criterion.

Cancer Drugs Fund

Pembrolizumab is not recommended for use in the Cancer Drugs Fund

3.15 The committee 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 company had not expressed an interest in the technology being considered for funding through the Cancer Drugs Fund. The committee noted that it had not been presented with any cost-effectiveness analyses based on its preferred assumptions and recalled that it had considered both the company's and ERG's cost-effectiveness analyses not appropriate for its decision making (see sections 3.12 and 3.13). Therefore, the committee agreed that, as it was unable to determine the most plausible ICERs, it was unable to determine whether pembrolizumab had the plausible potential to be cost effective for inclusion in the Cancer Drugs Fund. The Cancer Drugs Fund clinical lead said that, because KEYNOTE-048 was very mature (almost complete), making pembrolizumab available in the Cancer Drugs Fund would not generate data that would resolve any uncertainties. The committee

concluded that pembrolizumab (monotherapy and in combination) did not meet the criteria to be considered for inclusion in the Cancer Drugs Fund, so did not recommend it for use within the Cancer Drugs Fund.

Other factors

There are no equalities issues

3.16 No relevant equalities issues were identified.

There are no additional benefits not already captured in the economic analysis

3.17 The committee considered the innovative nature of pembrolizumab (monotherapy and in combination). The committee understood that improvements in survival and reduced adverse effects are important for people with this condition. The committee was aware of the impact of the disease on the person's carer and family (see section 3.1) and took this into account in its decision making. But it noted that no evidence was provided. It concluded that pembrolizumab (monotherapy and in combination) could be considered an important treatment option for this population, but there were no additional benefits associated with this treatment that had not been captured in the economic analysis.

Conclusion

The committee is minded not to recommend pembrolizumab (monotherapy or in combination) for metastatic or unresectable recurrent HNSCC

3.18 The committee agreed that KEYNOTE-048 was not wholly applicable to NHS practice (see section 3.5). Because current treatment options are different for cancer that started inside or outside the oral cavity, the committee concluded that it would like to see all clinical and cost-effectiveness analyses by primary tumour location. In addition, it had concerns about whether the baseline patient characteristics were balanced for the 2 subgroups of people whose cancer started inside or outside the oral cavity (see sections 3.6 and 3.10), and the utility value for progressed disease used in the economic model (see section 3.11). The

committee concluded that it was minded not to recommend pembrolizumab (monotherapy or in combination) as an option for metastatic or unresectable recurrent HNSCC. The committee said that it would like to see further analyses from the company, and it recommended that NICE requests these analyses (see section 1.2), which should be made available for the next appraisal committee meeting.

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.

Lindsay Smith
Chair, appraisal committee
January 2020

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Stephen Robinson
Technical lead

Nicola Hay
Technical adviser

Gemma Barnacle
Project manager

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