NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

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

1 Recommendations

1.1 Pembrolizumab is recommended 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. This is only if:

- pembrolizumab is given as a monotherapy
- pembrolizumab is stopped at 2 years of uninterrupted treatment, or earlier if disease progresses, and
- the company provides pembrolizumab according to the commercial arrangement (see section 2).

1.2 This recommendation is not intended to affect treatment with pembrolizumab that was started in the NHS before this guidance was published. People having treatment outside 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

Treatment of metastatic or unresectable recurrent HNSCC depends on where it starts. If it starts in the oral cavity (mouth), it is usually first treated with cetuximab

combination therapy (cetuximab with platinum and 5-FU [5-fluorouracil] chemotherapy). If it starts outside the oral cavity it is treated with chemotherapy (platinum and 5-FU) alone.

Clinical trial evidence from people who have HNSCC that expresses a biomarker called PD-L1 (with a CPS of 1 or more) shows that, if their cancer started in the oral cavity, pembrolizumab monotherapy works at least as well as cetuximab combination therapy and has lower overall costs. If their cancer started outside the oral cavity, pembrolizumab monotherapy works better than chemotherapy alone. It has higher overall costs but the cost-effectiveness estimates are within the range that NICE normally considers an acceptable use of NHS resources. Pembrolizumab monotherapy is therefore recommended for both types of HNSCC.

The cost-effectiveness estimates for pembrolizumab combination therapy compared with monotherapy, in both types of HNSCC, are higher than what NICE normally considers an acceptable use of NHS resources. Therefore it is not recommended.

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

Price

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

2.4 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 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.

Clinical need

A new treatment option is needed for people with metastatic or unresectable recurrent head and neck squamous cell carcinoma

3.1 The patient experts' submission stated that metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) has a big impact on the people living with the disease, and their carers and family. Having a complete response to treatment, being progression free for as long as possible, and having better quality of life are 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, including cetuximab, which may cause rash, diarrhoea and

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

People who would be offered pembrolizumab monotherapy or combination therapy are not clinically distinct populations

3.2 The marketing authorisation for pembrolizumab is as a monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy. The company did not provide evidence of a clearly defined population for whom pembrolizumab monotherapy would not be appropriate and pembrolizumab combination therapy would be offered instead, or vice versa. 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 states that the frequency of adverse reactions with combination therapy is higher than with pembrolizumab monotherapy. It says: 'Physicians should consider the benefit/risk balance of the available treatment options (pembrolizumab monotherapy or pembrolizumab in combination with chemotherapy) before initiating treatment in patients with HNSCC whose tumours express PD-L1'. The committee accepted that the decision about whether someone is offered monotherapy or combination is made on a case-by-case basis. Several clinical factors are considered. Some apply to both groups, such as good performance status, but there are factors that vary depending on the person, such as 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 yet possible to clearly define distinct patient populations who would be offered one treatment over the other.

Cetuximab combination therapy is a relevant comparator for cancer starting in the oral cavity, while chemotherapy alone is relevant for cancer starting outside the oral cavity

3.3 The clinical experts explained that people with metastatic or unresectable recurrent HNSCC have either cetuximab combination therapy (cetuximab with platinum and 5-FU chemotherapy) or chemotherapy (platinum and 5-FU) alone. People whose cancer started in the oral cavity are offered cetuximab combination therapy 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 combination therapy because of toxicity. They are offered chemotherapy alone. People whose cancer started outside the oral cavity are offered chemotherapy alone. After failure of first-line treatment, people may be offered 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, as a monotherapy or in combination with chemotherapy, was for the first-line treatment of metastatic or unresectable recurrent HNSCC regardless of where the tumour started. The committee agreed that cetuximab combination therapy was the relevant comparator for pembrolizumab for people whose cancer started in the oral cavity. This is because it is consistent with existing NICE technology appraisal guidance, and 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 chemotherapy alone was the relevant comparator for pembrolizumab for people whose cancer started outside the oral cavity. It acknowledged that this population has limited treatment options because cetuximab is only available for those whose cancer started in the oral cavity.

Pembrolizumab monotherapy and combination therapy should also be compared with each other

3.4 The committee agreed that, because it was not possible to clearly define distinct patient populations who would be offered pembrolizumab monotherapy and pembrolizumab combination therapy (see section 3.2), the 2 treatments should also be compared with each other (for both subgroups: people whose cancer started inside or outside the oral cavity).

Clinical evidence

The key clinical trial, KEYNOTE-48, is not wholly applicable to clinical practice in the NHS

3.5 The clinical evidence for pembrolizumab came from the ongoing KEYNOTE-048 randomised controlled trial. People in the trial had metastatic or unresectable recurrent HNSCC and were randomised to receive pembrolizumab monotherapy (n=301), pembrolizumab combination therapy (with chemotherapy; n=281) or cetuximab combination therapy (n=300). After disease progression people were able to have further treatment, including the anti-PD-L1 drug nivolumab. Because nivolumab is only available in the NHS through the Cancer Drugs Fund (see NICE's technology appraisal guidance for nivolumab for HNSCC), it cannot be considered as a comparator in this appraisal. The company adjusted the overall survival data to account for this by using the simplified 2-stage method. 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 metastatic or unresectable recurrent 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 combination therapy. In the NHS, these people are offered chemotherapy alone (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 in combination) in that subgroup. But it accepted the advice from clinical experts, submitted in response to the appraisal consultation document, that this is unlikely to overestimate the relative efficacy of pembrolizumab, and might potentially underestimate it (see also section 3.8).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 the NHS.

Pembrolizumab's clinical effectiveness should be considered separately for cancer starting inside or outside the oral cavity

3.6 The company submitted evidence for the PD-L1 with a CPS of 1 or more trial population, based on a prespecified subgroup analysis of KEYNOTE-048, in line with its marketing authorisation. Analysis for this population showed that pembrolizumab (monotherapy and in combination) extended overall survival compared with cetuximab combination therapy in people with a CPS of 1 or more. The hazard ratios were 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 combination therapy. However, the committee agreed that, because current treatment options in the NHS are different for cancer that started inside or outside the oral cavity (see section 3.3), it was appropriate to consider the clinical effectiveness of pembrolizumab in those 2 population subgroups. The committee also recalled the conclusion in existing NICE technology appraisal guidance on cetuximab for HNSCC that cetuximab combination therapy might be more effective in people whose cancer started in the oral cavity. Because the efficacy of cetuximab may differ depending on where the cancer has started, the committee agreed it was appropriate to consider the clinical data separately for each subgroup. The company stated that there is no scientific rationale to suggest pembrolizumab would work differently depending on where the

cancer started. But in response to the appraisal consultation document, it provided overall survival results from KEYNOTE-048 for the 2 subgroups (these results are confidential and therefore cannot be reported in detail here). The committee noted that the relative efficacy of pembrolizumab (monotherapy or in combination) may be different in the 2 subgroups, which could be because of the differences in the efficacy of pembrolizumab or cetuximab combination therapy, or because the trial was not designed to analyse differences between the subgroups. The committee also noted that the Kaplan–Meier curves for overall survival for pembrolizumab (monotherapy and in combination) and cetuximab combination therapy crossed over for the subgroup of people whose cancer started in the oral cavity, and the confidence intervals around the hazard ratio included 1. But this was not seen in the cancer starting outside the oral cavity. The committee also noted that, in both subgroups, pembrolizumab combination therapy appeared to offer a small clinical benefit over pembrolizumab monotherapy. The company and the ERG explained that the 2 subgroup analyses should be considered with caution because they were post-hoc analyses not powered to show differences between treatments. The committee concluded that, despite their limitations, subgroup analyses are the most appropriate source of clinical-effectiveness evidence for pembrolizumab decision making.

Clinical-effectiveness outcomes in the subgroups are uncertain because they do not account for potential imbalances in baseline characteristics

3.7 The company also provided the baseline characteristics for both subgroups, in response to a committee request to adjust for any imbalances. The Cancer Drugs Fund clinical lead advised that the modest imbalances in some characteristics would not favour either the pembrolizumab or comparator arms of the trial, but noted that the sample sizes being compared were small. The company explored methods to account for potential imbalances. It concluded that no variables needed to be adjusted for, because all variables had overlapping confidence intervals and there were no obvious baseline differences between

treatment groups or subgroups. The company also explained that adjusting for unnecessary confounders could introduce additional uncertainty and bias. The committee noted that no characteristic had a statistically significant effect on the overall survival hazard ratio for pembrolizumab (monotherapy or in combination) compared with cetuximab combination therapy. However, the committee noted that the lack of statistical significance is to be expected when making small, underpowered comparisons. It considered that characteristic imbalances should still be adjusted for when analysing clinical effectiveness in the 2 subgroups. The committee also noted that the company's analysis only explored the impact of baseline characteristics on relative treatment effectiveness, and did not consider whether any were prognostic factors that could affect clinical outcomes regardless of treatment. The committee agreed that the analyses provided by the company did not fully satisfy what it had requested, meaning the clinical-effectiveness outcomes were uncertain, and the extent and direction of this uncertainty was not known. The committee concluded that it would consider this uncertainty in its decision making.

Indirect treatment comparisons

The relative effectiveness of pembrolizumab and chemotherapy alone in people with cancer starting outside the oral cavity is uncertain

3.8 There was no direct evidence comparing pembrolizumab (monotherapy and in combination) with chemotherapy alone, which is the relevant comparator for cancers that started outside the oral cavity. For the whole PD-L1 positive CPS 1 or more HNSCC population, the company did a fractional polynomial network meta-analysis to compare pembrolizumab (monotherapy and in combination) with chemotherapy alone. However, this approach was not possible for the subgroup analyses because clinical-effectiveness data specific to cancer starting outside the oral cavity were not available from the key trial comparing cetuximab combination therapy with chemotherapy alone (EXTREME study).

Instead, the company used the ERG's preferred approach, using Kaplan–Meier data from the cetuximab combination therapy arm of KEYNOTE-048 as a proxy for chemotherapy alone for people whose cancer started outside the oral cavity. The clinical experts agreed that this approach was reasonable because the EXTREME trial showed a benefit from cetuximab combination therapy, compared with chemotherapy alone, only in cancers that started in the oral cavity. However, the Cancer Drugs Fund clinical lead advised that this approach may overestimate the effectiveness of platinum and 5-FU chemotherapy. The committee concluded that using cetuximab data to model outcomes for chemotherapy alone in the subgroup of people whose cancer started outside the oral cavity is subject to uncertainty, but it is the only available evidence for decision making.

Cost-effectiveness considerations

The 2-year stopping rule and company's modelling approach are appropriate for decision making

3.9 The company presented a 3-state partitioned survival model (progression free, progressed disease and death) comparing pembrolizumab (monotherapy or in combination) with cetuximab combination therapy or chemotherapy alone. 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. However, the 2-year stopping rule was consistent with the KEYNOTE-048 study design, and 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 and accepted the 2-year stopping rule.

A 5-year treatment benefit for pembrolizumab is appropriate

3.10 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 a treatment effect over 5 years (that is, applying a hazard ratio of 1 to both the pembrolizumab and cetuximab combination therapy arms 5 years after starting treatment, which is 3 years after stopping treatment). The clinical experts said that conceptually it was possible that pembrolizumab's treatment effect could last up to 10 years because immunotherapies such as pembrolizumab have a different mechanism to cytotoxic therapies. Once anti-tumour immunotherapy occurs, it is plausible that the effect of treatment could be maintained. But the experts highlighted that this was only speculative because there were 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. It noted that the ERG's proposed 5-year treatment duration was consistent with NICE's technology appraisal guidance for nivolumab for HNSCC. The committee concluded that assuming a 5-year treatment effect duration was more appropriate, and consistent with the previous head and neck cancer immunotherapy appraisal.

The Weibull functions are appropriate for modelling overall survival in both subgroups

3.11 Because pembrolizumab's cost effectiveness should be considered separately for cancer starting in the oral cavity and in cancer starting outside (see section 3.6), the committee considered that overall survival

should also be modelled separately for the 2 subgroups. The company used a piecewise log-normal extrapolation of the Kaplan–Meier curve for overall survival from KEYNOTE-048 for pembrolizumab (monotherapy and in combination) in both subgroups. The ERG highlighted that using log-normal distributions resulted in clinically implausible long-term survival estimates, in which a small number of people were predicted to have lower mortality rates than the general population. The ERG explained that it preferred the Weibull extrapolations, because they gave more clinically plausible results. The committee concluded that the log-normal extrapolations gave clinically implausible results, and that the Weibull distribution was more appropriate for decision making.

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

3.12 The company used a utility value of 0.71 to model health-related quality of life in its base-case analysis 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 this utility value was derived from the EQ-5D questionnaire completed by patients in the KEYNOTE-048 trial and an appropriate UK value set, which is consistent with the NICE reference case. However, it agreed that this utility value was too high. The committee noted that health-related quality of life was measured in the trial 30 days after progression, but no later. It agreed that the values may be subject to informative censoring. This means the progressed disease utility values were only derived from patients who had progressed within the previous 30 days, which may overestimate the health-related quality of life of all people with progressed disease. The company explained that it is challenging to collect health-related quality of life data from terminally ill people with progressive disease. The committee noted that the company had applied time-to-death utility decrements, which resulted in progressively lower utility values in the final 180, 90 and 30 days before death (the exact values are

confidential and therefore cannot be reported here). The committee considered that, because the time-to-death utility decrements were derived from the KEYNOTE-048 trial, they were at the same risk of informative censoring. The committee considered a lower utility value of 0.66 that the company had sourced from published literature. It noted this value was from the Checkmate 141 trial for nivolumab after platinum chemotherapy, which is a later line of treatment. It agreed that these data represent a slightly different population than in the KEYNOTE-048 trial. The company stated that the Checkmate 141 trial would have been subject to the same informative censoring bias as KEYNOTE-048. The committee noted these limitations, but agreed that the company's preferred value of 0.71 was still too high because people with progressed metastatic disease are likely to be in poor health. The committee concluded that it preferred to use the lower utility value for progressed disease, sourced from published literature, but recognised that neither estimate was ideal.

A fully incremental analysis should be used to determine cost effectiveness

3.13 The committee recalled that it was not possible to clearly define distinct patient populations who would be offered pembrolizumab monotherapy or combination therapy (see section 3.2). It recalled that, because people who would be offered pembrolizumab monotherapy and combination therapy are not clinically distinct populations, it was appropriate to compare the 2 regimens with each other (see section 3.4). Therefore, a fully incremental analysis should be used to determine the cost effectiveness of each pembrolizumab regimen.

End of life

Pembrolizumab meets the end of life criteria for HNSCC, although this is less certain for cancer starting in the oral cavity

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. The committee recalled its decision to consider the 2 subgroups separately (cancer starting inside and outside the oral cavity; see section 3.6). The committee also noted that pembrolizumab was likely to meet both the short life expectancy and the extension of life criteria for the 2 subgroups (cancer starting inside or outside the oral cavity; the exact values are confidential and therefore cannot be reported here). However, it noted that this is less certain for cancer starting in the oral cavity because Kaplan–Meier curves for overall survival cross, and confidence intervals around the hazard ratio include 1. The committee concluded that pembrolizumab (monotherapy or in combination) meets the end of life criteria for cancer starting inside and outside the oral cavity.

Cost-effectiveness results

The cost-effectiveness results based on the whole trial population (PD-L1 CPS 1 or more) are not appropriate for decision making

3.15 The original company's and ERG's base-case analyses were based on the whole trial population (PD-L1 CPS 1 or more) and used:

- clinical data from the company's fractional polynomial network meta-analysis (company) or Kaplan–Meier data from the cetuximab combination therapy arm of KEYNOTE-048 (ERG) for the comparison of pembrolizumab with chemotherapy alone for people whose cancer started outside the oral cavity (see section 3.8)
- a 20-year (company) or 5-year (ERG) duration of treatment effect (see section 3.10)

- overall survival modelled using log-logistic and log-normal curves for pembrolizumab monotherapy and combination therapy, respectively (company), or Weibull curves for both pembrolizumab monotherapy and combination therapy (ERG) (see section 3.11)
- trial-based utility value for progressed disease state (company and the ERG; see section 3.12)
- pairwise comparisons (company) or fully incremental analysis (ERG; see section 3.13).

All cost-effectiveness analyses included the company's commercial arrangement for pembrolizumab. Neither the company's nor the ERG's base-case analyses included all of the committee's preferred assumptions (see section 3.16). Therefore, neither analysis was appropriate for its decision making, and the committee agreed not to consider them further.

Pembrolizumab monotherapy is a cost-effective use of NHS resources for people whose cancer started in the oral cavity

3.16 The committee's preferred modelling assumptions used:

- efficacy data from subgroup analyses (by cancer origin; see section 3.6, section 3.7 and section 3.11)
- a 5-year duration of treatment effect (see section 3.10)
- Weibull curves to model overall survival (see section 3.11)
- a lower baseline utility value for progressed disease (see section 3.12)
- fully incremental analysis (see section 3.13).

Using these assumptions, a revised confidential discount for pembrolizumab, and the confidential discount for cetuximab, pembrolizumab monotherapy dominated (that is, was more effective and cost less than) cetuximab combination therapy for people whose cancer started in the oral cavity. The committee recalled that the clinical-effectiveness data were uncertain, because they were from a

post-hoc subgroup analysis (see section 3.6) and had not been adjusted for imbalances in baseline characteristics (see section 3.7). It also recalled that the Kaplan–Meier curves for overall survival crossed over for this subgroup, and the confidence intervals around the hazard ratio included 1 (see section 3.6). The committee noted that the survival gain for pembrolizumab monotherapy over cetuximab combination therapy predicted by the model for this subgroup was caused by differences in the long-term extrapolations. However, it agreed that, even if the long-term survival gain was not realised in clinical practice, and instead the treatments were only equally effective, pembrolizumab monotherapy would still be dominant. The committee concluded that pembrolizumab monotherapy is a cost-effective use of NHS resources for people with metastatic or unresectable recurrent HNSCC whose cancer started in the oral cavity.

Pembrolizumab monotherapy is a cost-effective use of NHS resources for people whose cancer started outside the oral cavity

3.17 The committee recalled its preferred modelling assumptions (see section 3.16). Using these assumptions and a revised confidential discount for pembrolizumab, the most plausible fully incremental cost-effectiveness ratio (ICER) for people with cancer that started outside the oral cavity was below £50,000 per quality-adjusted life year (QALY) gained for pembrolizumab monotherapy compared with chemotherapy alone (the exact ICER is confidential and cannot be reported here). The committee recalled the high level of uncertainty in the clinical-effectiveness estimates, which were based on post-hoc subgroup analyses (see section 3.6) and had not been adjusted for imbalances in baseline characteristics (see section 3.7). However, it also recalled that using cetuximab data from KEYNOTE-048 may overestimate the effectiveness of chemotherapy alone (see section 3.8), although the magnitude of this is unknown. It recalled that people whose cancer started outside the oral cavity currently have limited treatment options because cetuximab is only available for those whose cancer started in the oral cavity (NICE's technology appraisal

guidance on cetuximab for HNSCC; see section 3.3). The committee was aware that only deterministic ICERs had been presented, but noted that probabilistic ICERs would be similar. The committee concluded that pembrolizumab monotherapy is likely to be cost effective for people with metastatic or unresectable recurrent HNSCC whose cancer started outside the oral cavity.

Pembrolizumab combination therapy is not cost effective for cancer that started inside or outside the oral cavity

3.18 The committee recalled its preferred modelling assumptions, and that fully incremental analysis should be used (see section 3.16). Using these assumptions and a revised confidential discount for pembrolizumab, the most plausible fully incremental ICERs for pembrolizumab combination therapy were substantially higher than £50,000, compared with pembrolizumab monotherapy, regardless of where the tumour started (the exact ICERs are confidential and cannot be reported here). The incremental cost of combination therapy was mainly because of the administration of chemotherapy, and it provided relatively little additional clinical benefit. Therefore, the committee concluded that pembrolizumab combination therapy is not cost effective for people with metastatic or unresectable recurrent HNSCC, regardless of where the tumour started.

Cancer Drugs Fund

Pembrolizumab combination therapy is not recommended for use in the Cancer Drugs Fund

3.19 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 Cancer Drugs Fund clinical lead advised that the KEYNOTE-048 trial data are very mature (almost complete), making it unlikely that using pembrolizumab combination therapy in the Cancer

Drugs Fund would generate data that would resolve any uncertainties for cancer starting inside or outside the oral cavity. The committee concluded that pembrolizumab combination therapy 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

3.20 No relevant equalities issues were identified.

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

3.21 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

Pembrolizumab monotherapy is recommended for HNSCC

3.22 The committee acknowledged that there is a clinical need for an effective treatment that improves quality of life for people with metastatic or unresectable recurrent HNSCC (see section 3.1). It also acknowledged that people whose cancer started outside the oral cavity currently have limited treatment options because cetuximab is only available for those whose cancer started in the oral cavity (NICE's technology appraisal

guidance on cetuximab for HNSCC; see section 3.3). 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 considered all clinical and cost-effectiveness analyses by primary tumour location (see section 3.6). It noted the limitations of post-hoc subgroup analyses (see section 3.6) and that imbalances in baseline patient characteristics for the 2 subgroups had not been adjusted for (see section 3.7). While accepting that these limitations introduced uncertainty, the committee agreed that the subgroup analyses provided the most appropriate source of clinical-effectiveness data to consider in its decision making. The committee also agreed that a lower utility value for progressed disease, sourced from published literature, more accurately represented the experience of people with progressed metastatic disease, who are normally in very poor health (see section 3.12). The committee also agreed that pembrolizumab monotherapy and combination therapy should be compared with each other in a fully incremental analysis, because people who would be offered each regimen are not clinically distinct populations (see section 3.2, section 3.4 and section 3.13). In summary, it concluded that pembrolizumab:

- monotherapy is a cost-effective use of NHS resources for people whose cancer started inside or outside the oral cavity, compared with cetuximab combination therapy or chemotherapy alone
- combination therapy is not a cost-effective use of NHS resources for people whose cancer started inside or outside the oral cavity, compared with pembrolizumab monotherapy.

Treatment with pembrolizumab should be stopped after 2 years of uninterrupted treatment, or earlier if disease progresses.

4 Implementation

4.1 Section 7(6) 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 untreated metastatic or unresectable recurrent

head and neck squamous cell carcinoma and their cancer started in the oral cavity, 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 Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication. 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
October 2020

6 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.

Ewa Rupniewska and Stephen Robinson
Technical leads

Jamie Elvidge and Nicola Hay
Technical advisers

Kate Moore and Gemma Barnacle
Project managers

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