NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung 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 with carboplatin and paclitaxel or nab-paclitaxel for treating metastatic squamous non-small cell lung cancer 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: September 2021

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: 30 September 2021

Second appraisal committee meeting: 14 October 2021

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

1 Recommendations

1.1 Pembrolizumab plus carboplatin and paclitaxel is not recommended, within its marketing authorisation, for untreated metastatic squamous non-small-cell lung cancer (NSCLC) in adults.

1.2 This recommendation is not intended to affect treatment with pembrolizumab plus carboplatin and paclitaxel that was funded by the Cancer Drugs Fund before final guidance was published. If this applies, when that funding ends, pembrolizumab plus carboplatin and paclitaxel will be funded by the company until the patient and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

This appraisal reviews the additional evidence collected as part of the Cancer Drugs Fund managed access agreement for pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel (pembrolizumab combination therapy) for untreated metastatic squamous NSCLC (NICE technology appraisal guidance TA600).

Untreated metastatic squamous NSCLC is usually treated with cisplatin or carboplatin plus either gemcitabine, paclitaxel or vinorelbine (platinum-based combination chemotherapy) in people whose tumours express PD-L1 at less than 50%, or pembrolizumab alone for people whose tumours express PD-L1 at 50% or more.

Clinical trial evidence shows that pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel increases how long people with metastatic squamous NSCLC live compared with placebo plus carboplatin and paclitaxel or nab-paclitaxel. But, in the NHS, carboplatin plus gemcitabine is the most commonly used platinum-based chemotherapy, and nab-paclitaxel is not available. Also, the evidence for people in the PD-L1 subgroups is uncertain, and pembrolizumab combination therapy has only been indirectly compared with pembrolizumab alone in people whose tumours express PD-L1 at 50% or more. So, the evidence does not capture how pembrolizumab combination therapy will be used in the NHS.

Pembrolizumab combination therapy is likely to meet the end of life criteria for people with a PD-L1 tumour proportion score of less than 50%. But it is unclear whether the end of life criteria is met in people with a PD-L1 tumour proportion score of 50% or more because of issues around generalisability for this group. The cost-effectiveness estimates are uncertain, and likely to be higher than what NICE considers an acceptable use of NHS resources. Therefore, pembrolizumab combination therapy is not recommended.

2 Information about pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel

Marketing authorisation indication

2.1 Pembrolizumab (Keytruda, Merck Sharp & Dohme) plus carboplatin and paclitaxel or nab-paclitaxel is indicated for 'the first-line treatment of metastatic squamous non-small-cell lung carcinoma in adults'.

2.2 Nab-paclitaxel is not commissioned by NHS England (see NICE technology appraisal 362 – terminated appraisal) and is therefore not considered as part of the appraisal recommendation.

Dosage in the marketing authorisation

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

Price

2.4 Pembrolizumab solution for infusion costs £2,630 per 100-mg vial (excluding VAT; BNF online, accessed August 2021).

2.5 The company has a commercial arrangement. This makes pembrolizumab available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. The size of the discount is commercial in confidence. It is the company's

responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

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

This review looks at data collected in the Cancer Drugs Fund to address uncertainties identified during the original appraisal of pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel (from now, pembrolizumab combination therapy) for untreated metastatic squamous non-small-cell lung cancer (NSCLC). Further information about the original appraisal is in the committee papers. As a condition of the Cancer Drugs Fund funding and the managed access arrangement, the company was required to collect updated efficacy data from the KEYNOTE-407 trial about overall survival in people with untreated metastatic squamous NSCLC. It was required to do this for the overall population and by PD-L1 tumour proportion score subgroups.

The appraisal committee was aware that no additional safety data from KEYNOTE-407 was presented for this Cancer Drugs Fund review. But it agreed this was unlikely to affect the cost-effectiveness estimates.

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

- uncertainty about the long-term treatment effect of pembrolizumab combination therapy on progression-free survival and overall survival
- the fact that committee's preferred assumptions about subsequent immunotherapy use did not reflect experience in KEYNOTE-407

- the fact that the indirect comparison for the subgroup with a PD-L1 tumour proportion score of 50% or more presented in the company submission to the Cancer Drugs Fund review was not robust
- uncertainty about whether pembrolizumab combination therapy meets NICE's end of life criteria.

Clinical need

Pembrolizumab combination therapy would be a welcome additional treatment option for untreated metastatic squamous NSCLC

3.1 People with squamous NSCLC often have a poor quality of life, and a potential extension to life is important to them. Outcomes tend to be worse with squamous NSCLC than with non-squamous NSCLC because people have a higher prevalence of smoking-related comorbidities. For people with squamous NSCLC whose tumours express PD-L1 with a tumour proportion score less than 50%, outcomes are particularly poor. This is because the only first-line treatment is platinum-based combination chemotherapy, if it is tolerated. In the original appraisal, the clinical experts explained that most clinicians would use pembrolizumab monotherapy for people whose tumours express PD-L1 at 50% or more to avoid chemotherapy toxicity. But they added that a few people who need a rapid response may benefit from initial combination therapy with pembrolizumab and chemotherapy (for example, those with impending major airway obstruction). They also commented that the role of biomarkers such as PD-L1 to predict the cancers most likely to respond to immunotherapy is less well established in squamous NSCLC than in non-squamous NSCLC. The committee concluded that pembrolizumab combination therapy would be a welcome additional treatment option for untreated metastatic squamous NSCLC.

Clinical management

Treatment and prognosis will differ by PD-L1 status so subgroups based on PD-L1 status should be considered separately

3.2 Treatment for lung cancer is defined by histology (non-squamous or squamous NSCLC) and PD-L1 tumour proportion score. This is in line with NICE's guideline on lung cancer: diagnosis and management. First-line management of metastatic squamous NSCLC in clinical practice is platinum-based combination chemotherapy (that is, cisplatin or carboplatin and either gemcitabine, paclitaxel or vinorelbine) for people whose tumours express PD-L1 at less than 50%. In NICE's technology appraisal guidance on pembrolizumab for untreated PD-L1-positive metastatic NSCLC, pembrolizumab (alone) is recommended only for people whose tumours express PD-L1 at 50% or more. The committee was also aware of the different treatment options for people whose tumours express PD-L1 at different levels (see section 3.1). The committee considered that treatment and prognosis will differ by PD-L1 status and concluded that subgroups based on PD-L1 tumour proportion scores should be considered separately.

Clinical evidence

Intention-to-treat results do not reflect clinical practice and decisions about clinical effectiveness should be based on PD-L1 status

3.3 The main clinical evidence for pembrolizumab combination therapy came from KEYNOTE-407, a randomised placebo-controlled trial. It included 559 adults with untreated advanced or metastatic squamous NSCLC with an Eastern Cooperative Oncology Group performance status of 0 or 1. Pembrolizumab combination therapy was compared with placebo plus carboplatin and paclitaxel or nab-paclitaxel (from now, standard chemotherapy) as a first-line treatment. In NHS clinical practice, carboplatin plus gemcitabine is the most commonly used chemotherapy regimen for people whose tumours express PD-L1 at less than 50%. Also,

nab-paclitaxel is not commissioned by NHS England. In its submission to the Cancer Drugs Fund review, the company provided additional overall and progression-free survival data from the final analysis of KEYNOTE-407 (data cut May 2019). Median overall survival was 17.1 months for pembrolizumab combination therapy and 11.6 months for standard chemotherapy (hazard ratio [HR] 0.71, 95% confidence interval [CI] 0.58 to 0.88). Median progression-free survival was 8.0 months for pembrolizumab combination therapy and 5.1 months for standard chemotherapy (HR 0.57, 95% CI 0.47 to 0.69). At response to technical engagement, the company provided additional overall survival data from a later follow up of KEYNOTE-407 (data cut September 2020). It wanted the committee to consider data only from the whole intention-to-treat population rather than from the PD-L1 subgroups. Median overall survival was 17.2 months for pembrolizumab combination therapy and 11.6 months for standard chemotherapy (HR 0.71, 95% CI 0.59 to 0.86). Median progression-free survival was 8.0 months for pembrolizumab combination therapy and 5.1 months for standard chemotherapy (HR 0.59, 95% CI 0.49 to 0.71). The committee agreed that overall and progression-free survival data from the final analysis and additional data cuts were more mature than those from the interim analysis used in the original appraisal. It recognised that pembrolizumab combination therapy improved overall and progression-free survival compared with standard chemotherapy in the intention-to-treat population. However, it acknowledged that the results are not generalisable to clinical practice. This was because the treatments used in the study were different to those used in the NHS, depending on the level of PD-L1 tumour proportions (see sections 3.2 and 3.4). The committee concluded that the clinical results used in the intention-to-treat population did not reflect clinical practice. It further concluded that decisions about clinical effectiveness should be based on PD-L1 status (that is, PD-L1 tumour proportion scores of less than 50% and 50% or more).

Pembrolizumab combination therapy is likely to be clinically effective but the effect might differ depending on PD-L1 tumour proportion score

3.4 Pembrolizumab combination therapy is likely to be clinically effective in the PD-L1 subgroups, but the overall survival estimates are less certain. The company presented clinical-effectiveness results for the PD-L1 subgroups in its submission. The committee was aware that, in the protocol for KEYNOTE-407, people were stratified to treatment arms by a PD-L1 tumour proportion score of at least 1% and less than 1%. However, people were enrolled regardless of PD-L1 status and were spread across 3 PD-L1 tumour proportion score subgroups (less than 1%, 1% to 49%, and at least 50%). The final analysis of KEYNOTE-407 (data cut May 2019) showed:

- a 21% reduction in risk of death for people with a PD-L1 tumour proportion score of less than 1% (HR 0.79, 95% CI 0.56 to 1.11)
- a 41% reduction for people with PD-L1 tumour proportion scores of 1% to 49% (HR 0.59, 95% CI 0.42 to 0.84)
- a 21% reduction for people with a PD-L1 tumour proportion score of 50% or more (HR 0.79). The confidence intervals and median overall and progression-free survival values are academic in confidence so cannot be reported here.

The committee agreed that pembrolizumab combination therapy was effective at increasing progression-free survival in all PD-L1 subgroups. It was also effective at reducing risk of death in people with PD-L1 tumour proportion scores of 1 to 49%. The results for people with PD-L1 tumour proportion scores of less than 1% and 50% or more were less statistically certain. The committee noted the comparator in the trial for people with PD-L1 tumour proportion scores of 50% or more did not reflect that in clinical practice. It also noted the population included in the trial would not specifically be those who needed a rapid treatment response because of an urgent clinical need (see section 3.1). The company's original position had been that the evidence would be considered for the PD-L1 biomarker

based on the 3 PD-L1 subgroups (less than 1%; 1% to 49% and at least 50%). The committee noted that the trial design of KEYNOTE-407 did not directly reflect clinical practice. In the original appraisal, the ERG had highlighted that KEYNOTE-407 may have benefitted from including an additional study arm for pembrolizumab monotherapy for people with a PD-L1 tumour proportion score of 50% or more. This would have allowed pembrolizumab combination therapy to be compared with pembrolizumab monotherapy in people whose cancer is known to respond to it. The committee agreed that stratifying clinical evidence by these 3 PD-L1 subgroups was not generalisable to NHS clinical practice (see section 3.2). It would have preferred to see the results of the PD-L1 subgroups more closely aligned to the treatment options provided in the NHS. That is, for people with a PD-L1 tumour proportion score of less than 50% and 50% or more. The committee acknowledged that there would be uncertainties associated with this because:

- KEYNOTE-407 was not stratified in this way
- any analysis that attempts to blend the subgroups can potentially break randomisation.

The committee concluded that pembrolizumab combination therapy is likely to be clinically effective compared with platinum-based chemotherapy for people with PD-L1 tumour proportion score of less than 50%. However, there is uncertainty over the exact overall survival estimates because of the how the subgroups were stratified. The committee further concluded that for people with tumours expressing PD-L1 at 50% or more in the KEYNOTE-407 trial, the results were not generalisable to NHS clinical practice.

The company's economic model

The company's updated economic model is generally robust for decision making but could have more closely reflected clinical practice

3.5 At the original appraisal committee meeting, the committee agreed that it preferred several amendments to the company model. For its updated economic analysis, the company used as the starting point the ERG's preferred analysis that was used in the original appraisal. This used the more conservative clinical estimates around progression-free-survival as agreed by the committee (termed the 'ERG's pessimistic analysis 6b'). In its submission to the Cancer Drugs Fund review, the company made several changes to its updated model. These included the following amendments, which it applied to the final data cut of KEYNOTE-407:

- Log-logistic parametric models were used to extrapolate overall survival in each treatment group.
- A hybrid approach was used that included Kaplan–Meier estimates followed by log-normal extrapolation models with a 26-week cut-off point to extrapolate progression-free survival in each treatment group.
- A generalised gamma extrapolation model (shortened to a maximum treatment duration of 35 cycles) was used to model time to treatment discontinuation for pembrolizumab, and Kaplan–Meier estimates were updated for the standard care group.
- The probabilities of having second-line treatments were updated. Also, the data used to model assumptions around the duration of second-line atezolizumab and pembrolizumab in the standard care group (previously based on KEYNOTE-407) was updated to include the OAK and KEYNOTE-010 trials.
- Health utilities were defined according to the model health states. The progression-free state was based on KEYNOTE-407 and the post-progression state was based on the TOPICAL trial with adjustment for the number of people having second-line treatment.

- Time-varying hazard ratios from KEYNOTE-407 and KEYNOTE-042 were used to estimate the indirect treatment comparison of pembrolizumab monotherapy and pembrolizumab combination therapy for people with a PD-L1 tumour proportion score of 50% or more.

The committee agreed that, overall, these amendments were in line with the terms of engagement for the Cancer Drugs Fund review. It also agreed that the company's updated model was generally robust for decision making. The committee recognised that the company had focused the cost-effectiveness estimates on the intention-to-treat population. However, it would have preferred to see the economic model replicate clinical practice by basing the cost-effectiveness estimate on the PD-L1 subgroups seen in clinical practice. The committee concluded that the company's economic model was generally robust for decision making but could have more closely reflected clinical practice.

Modelled overall survival estimates for people with a PD-L1 tumour proportion score of 50% or more are highly uncertain

3.6 Pembrolizumab monotherapy is the standard first-line treatment option for people with a PD-L1 tumour proportion score of 50% or more. So, the company did an indirect treatment comparison of pembrolizumab combination therapy and pembrolizumab monotherapy using data from KEYNOTE-407 and KEYNOTE-042. It used this to inform the economic analysis for pembrolizumab combination therapy. KEYNOTE-042 was a trial including 1,274 people with PD-L1 positive tumours that compared pembrolizumab monotherapy with platinum-based chemotherapy. The ERG noted there were several technical difficulties with the methods used in the company's model. The company provided the following re-analyses at the clarification stage to try and resolve these difficulties:

- recensoring for the control arms of KEYNOTE-407 and KEYNOTE-042
- using the failure odds transformation of the log-logistic distribution

- including population adjustment without a treatment-switching adjustment
- including both population adjustment and a treatment-switching adjustment.

The committee was aware that the re-analyses resolved the ERG's concerns around the technical robustness of the company's methods. However, it thought that uncertainties still remained about the treatment effect of pembrolizumab monotherapy compared with pembrolizumab combination therapy. The ERG noted that the results of the indirect treatment comparison suggested a consistent, general trend of a treatment effect that always favoured pembrolizumab monotherapy. This was regardless of which method of analysis was chosen. However, the ERG acknowledged that these estimates were highly uncertain because the 95% confidence intervals crossed 1.0. The committee recalled that other technology appraisals have suggested similar effects. Results from the indirect treatment comparison in NICE's technology appraisal guidance on pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer showed no statistically significant difference in the overall survival estimates for pembrolizumab combination therapy compared with monotherapy. In fact, in that appraisal, although the point estimate suggested better overall survival for pembrolizumab combination therapy, the 95% credible interval showed that this was not statistically significant. The committee concluded that the modelled overall survival estimates for people with a PD-L1 tumour proportion score of 50% or more were highly uncertain.

The company's choice of parametric models for overall and progression-free survival are appropriate for decision making

3.7 In the original appraisal, the company and the ERG used various modelling approaches to estimate long-term survival in both the pembrolizumab combination therapy and the comparator arms. The

company fitted a hybrid model using Kaplan–Meier data from the interim analysis of KEYNOTE-407 and additional data from the Surveillance, Epidemiology, and End Results (SEER) database. The committee had concluded that the company's modelled overall survival in the pembrolizumab combination therapy arm was too optimistic. It preferred the ERG's log-logistic extrapolation in each treatment arm with no cut-off points. This was because data in the SEER database had not included second-line immunotherapy treatments. In its submission to the Cancer Drugs Fund review, the company fitted a log-logistic model to the final analysis (May 2019 data cut) of KEYNOTE-407 with no cut-off points to the data for each treatment group. The company justified this choice because it was in line with the committee's preferred analyses from the original appraisal. It also had one of the best goodness-of-fit statistics, and the most clinically plausible 5-year and 10-year overall survival estimates. The committee noticed that, overall, the Weibull extrapolation model had one of the best statistical fits. However, it considered that the differences were marginal. For the updated model, the company fitted the same hybrid model to extrapolate progression-free survival as it used in its original model, using the final analysis data cut off. At technical engagement, the company provided additional survival follow-up data (based on a cut-off date of September 2020) to reinforce the overall and progression-free survival estimates. The company did not incorporate the Kaplan–Meier estimates using the most recent data cut-off plots into its economic model. The ERG was able to provide these updated overall survival extrapolations using the latest cut-off data. However, it was not able to do so to update progression-free survival because that had been based on a hybrid model, which the company had not updated. The ERG carried out additional sensitivity analyses using alternative parametric survival models. The committee recognised that all the estimates were subject to uncertainty. It also noted that using the alternative parametric survival models did influence the incremental cost-effectiveness ratio (ICER) for pembrolizumab combination therapy. The committee noted

that, with the exception of the log-normal extrapolation model, the ICER would increase if any other extrapolation model was used to model both overall and progression-free survival. However, the ICER was less sensitive to the choice of progression-free survival model. The committee concluded the company's choice of parametric models was appropriate for decision making.

Costs of subsequent treatment included in the economic model should reflect the treatments in KEYNOTE-407

3.8 The company's updated economic model submitted to the Cancer Drugs Fund review assumed that the costs of subsequent immunotherapies applied to everyone having standard care and subsequent-line treatment. This was in line with the committee's preferred assumptions from the original appraisal about subsequent-line immunotherapy in the standard chemotherapy group. But the ERG noted that this was inconsistent with the experience of people in KEYNOTE-407, in which a few people had chemotherapy alone as subsequent treatment. It also noted that the model overestimated the costs of second-line immunotherapy in the standard care group, which would underestimate the ICER for pembrolizumab combination therapy. The ERG used an alternative approach in its preferred base case, in which the costs of chemotherapy were only applied to people who had subsequent-line treatment. This included the people in KEYNOTE-407 who had subsequent chemotherapy. The clinical experts explained that this did not reflect clinical practice. The committee noted that, although including costs for subsequent-line chemotherapy differed from usual clinical practice, it preferred the consistent approach used by the ERG. The committee agreed that the costs of subsequent treatment included in the economic model should have reflected the treatments in KEYNOTE-407.

A treatment effect lasting between 3 and 5 years is appropriate for decision making

3.9 In the original appraisal, the company's base case included a 2-year treatment stopping rule. At that time, the committee was aware that the maximum possible treatment duration with pembrolizumab combination therapy in KEYNOTE-407 was 35 cycles (2 years of treatment). It had concluded that stopping treatment at 2 years was acceptable. The company's original model also assumed a lifetime treatment effect after stopping treatment. This was based on the rationale that there is no evidence that treatment effect wanes after treatment is stopped. The committee had considered that the lifetime treatment effect of pembrolizumab combination therapy was implausible. It thought that a treatment effect lasting between 3 and 5 years was more appropriate. In its submission to the Cancer Drugs Fund review, the company proposed a 5-year duration of treatment benefit for overall survival in its base case. It suggested that there was no direct evidence to support the suggestion that the treatment benefit will wane 5 years after stopping treatment. However, it chose this for consistency with previous immunotherapies. The company included scenario analyses exploring the effects of 3-year and 4-year durations of treatment effect. The ERG noted that the waning of treatment effect in the company's base case had only been applied to progression-free survival in the subgroup of people with PD-L1 tumour proportion scores of 50% or more. So, it applied the waning of treatment effect to both overall and progression-free survival in its preferred base case. The committee noted that including waning of treatment effect on progression-free survival for the intention-to-treat population did not have a large effect on the ICER. The committee considered the company's and ERG's preferred assumptions alongside decisions made in previous technology appraisals of immunotherapies. The committee agreed there was no new evidence presented to change its position from the original appraisal. So, the committee concluded that, for consistency with previous appraisals of immunotherapies for NSCLC, a treatment effect lasting

between 3 and 5 years after starting treatment was appropriate for decision making.

Time to treatment stopping for both groups should be modelled using cumulative probabilities from the Kaplan–Meier estimates

3.10 The company considered various survival extrapolation models fitted to the final data cut of KEYNOTE-407 to model time to stopping treatment for the pembrolizumab combination arm. It chose to use the generalised gamma distribution in its base case, based on goodness-of-fit statistics. The company did not fit parametric models for the comparator group. But, in line with the company model for the original appraisal, it used Kaplan–Meier estimates based on the observed cumulative probabilities of staying on treatment. These were taken from the final data cut of KEYNOTE-407. The ERG had no concerns with this approach for the standard care group. But it considered the extrapolation modelling approach used for the pembrolizumab arm had not fitted the data well. It chose to use the cumulative probabilities from the Kaplan–Meier estimates in its preferred base case analysis. The committee agreed that the methods used to modelling time to stopping treatment in the ERG's base case were preferable to fitting survival models that did not represent the data well. For this reason, the committee concluded that time to stopping treatment for both treatment groups should be modelled using cumulative probabilities from the Kaplan–Meier estimates.

End of life

The extension to life criterion is likely met for the subgroup with a PD-L1 score of less than 50% but it is less clear for those above 50%

3.11 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. This states that a NICE technology appraisal committee should satisfy itself that all of the following criteria have been met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally at least an additional 3 months, compared with current NHS treatment.

The committee recognised that the overall survival data from the latest data cut showed the survival benefit with pembrolizumab combination therapy was maintained (HR 0.71) in the intention-to-treat population. This suggests a median overall survival of 5.6 months with pembrolizumab combination therapy compared with standard care. However, the survival benefit was more uncertain in the PD-L1 subgroups. The hazard ratios for overall survival were higher in the subgroup with a PD-L1 tumour proportion score of 50% or more (HR 0.79). The confidence intervals crossed 1.0, suggesting that there may not be a difference between pembrolizumab combination therapy and standard care. The committee noted that it had not seen the results stratified for people with PD-L1 tumour proportion scores of less than 50% and 50% or more. It recalled that the comparator in clinical practice is pembrolizumab monotherapy for people with a PD-L1 tumour proportion score of 50% or more. It also noted that the cost-effectiveness estimates had shown that life years would be lost in all scenarios in which pembrolizumab combination therapy was compared with pembrolizumab monotherapy. The committee also noted the data used to compare people with PD-L1 tumour proportion scores of 50% or more came from the company's indirect treatment comparison. This had been based on KEYNOTE-407 and KEYNOTE-042. The committee noted the populations included in both of these trials included people with PD-L1 positive tumours. But the inclusion criteria did not directly align specifically with people who would need an urgent clinical response. The committee was more cautious in interpreting the extension to life criterion to this population. It concluded that pembrolizumab combination therapy would likely meet the extension to life criterion for people with a PD-L1 tumour proportion score of less than

50%. It also concluded that it was less clear whether this criterion would be met for those with a PD-L1 tumour proportion score of 50% or more because of the issue with generalisability of the trials for this group.

The short life expectancy criterion is likely met for the subgroup with PD-L1 scores of less than 50%, but not for the subgroup with scores of 50% or more

3.12 For the short life expectancy criterion, the company noted that the most recent data from KEYNOTE-407 (data cut September 2020) reported a median overall survival of 11.6 months for the standard care arm for the intention-to-treat population. The company model predicted a mean overall survival with standard care of 27.1 months. In its response to technical engagement, the company suggested that the end of life criteria should only be applied to the intention-to-treat population. Based on the most recent overall survival data, it noted that its economic model predicted that only 28.5% of people in the intention-to-treat population having standard chemotherapy would be alive at 24 months. The committee noted the model predicted that 40.3% of those having pembrolizumab combination therapy would be alive at 24 months compared with 28.5% of those having standard chemotherapy. However, the Kaplan–Meier estimates from the trial were less clear; these suggested that 30.8% of people having standard chemotherapy and 36% having pembrolizumab combination therapy would be alive at 24 months. The company noted that survival with current therapies in NICE's ongoing technology appraisal for nivolumab with ipilimumab and chemotherapy for untreated metastatic non-small-cell lung cancer is less than 24 months for people with squamous histology and a PD-L1 tumour proportion score of less than 50%. This had been supported by the clinical experts involved in that technology appraisal, who confirmed that treatment options in the NHS would vary by histology and PD-L1 status. The company suggested that NICE's end of life criteria should not be stratified by PD-L1 subgroups. This was because the trial protocol for KEYNOTE-407 did not

stratify by PD-L1 subgroups of greater or less than 50%. The committee acknowledged that the Cancer Drugs Fund limits pembrolizumab combination therapy use in people with PD-L1 tumour proportion scores of 50% or more to those who need an urgent clinical response only. The ERG noted that use in that proposed subgroup was not specifically reflected in the populations included in the company's economic comparison. That included everyone in KEYNOTE-407 and in KEYNOTE-042 with a PD-L1 tumour proportion score of 50% or more, but not specifically people who need an urgent clinical response. As such, the company's cost-effectiveness estimates for this subgroup may not have been meaningful. The committee noted that the company's modelled overall survival estimates were around 2 years for everyone with a PD-L1 score of less than 50%. The committee agreed that the short life expectancy criterion for the PD-L1 subgroup with tumour proportion scores of less than 50% may have been met. It agreed that the short life expectancy criterion had not been met in the PD-L1 subgroup with tumour proportion scores of 50% and over. This is because this group would usually be given pembrolizumab monotherapy in NHS clinical practice, which was not done in either KEYNOTE-407 and KEYNOTE-042. The committee noted that the company's modelled overall survival estimates for this group was substantially higher than 2 years. It concluded that the short life expectancy criterion was likely met for people with a PD-L1 score of less than 50%, but not for the PD-L1 subgroup with tumour proportion scores 50% and over.

Cost-effectiveness estimates

Pembrolizumab combination therapy is not a cost-effective use of NHS resources

3.13 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 company's base-case model gave a deterministic ICER of £25,431 per QALY gained for pembrolizumab combination therapy compared with standard care based on the intention-to-treat population. This included a commercial access agreement for pembrolizumab. The ICER was considerably higher when considering any comparator patient access schemes. These values are commercial in confidence and so cannot be reported here. The committee's preferred assumptions included:

- log-logistic extrapolation fitted to overall survival in both treatment arms
- a hybrid model fitted for progression-free survival in both treatment arms
- cumulative probabilities from the Kaplan–Meier estimates fitted to time to treatment discontinuation data in both arms
- utilities based on pre- or post-progression status
- a stopping rule and costs applied for 35 cycles
- duration of subsequent treatments in line with the company submission to the Cancer Drugs Fund review and updated distribution of subsequent-line therapies in line with subsequent treatments in KEYNOTE-407
- a waning of treatment effect for both overall and progression-free survival and a treatment effect lasting between 3 and 5 years after starting treatment
- stratification by PD-L1 subgroups with tumour proportion scores of less than 50% and at least 50%.

The company's base case included cost-effectiveness estimates based on 3 PD-L1 subgroups (PD-L1 tumour proportion score of less than 1% 1%

to 49% and at least 50%). The committee recalled that it had considered this subgroup stratification not to be relevant to NHS clinical practice. Rather, it would have preferred cost-effectiveness estimates for PD-L1 tumour proportion scores of less than 50% and 50% or more. The ERG provided exploratory analyses using a weighted value to include PD-L1 tumour proportion scores of less than 1% and of 1% to 49% in a weighted value of PD-L1 tumour proportion score of less than 50%. However, the committee noted the high levels of uncertainty in relying on these weighted estimates. The committee noted all cost-effectiveness estimates were based on the assumption that waning of treatment effect occurred at 5 years. It noted this was likely to underestimate the ICER for pembrolizumab combination therapy compared with its preferred inclusion of a 3 to 5 year waning of treatment effect. The committee considered that the ICERs for the PD-L1 subgroup with tumour proportion scores of less than 50% were above what is normally considered a cost-effective use of NHS resources. When different efficacy was assumed for the PD-L1 subgroup with tumour proportion scores of 50% or more, the cost-effectiveness estimate for pembrolizumab combination therapy was in the south-west quadrant of the cost-effectiveness plane in the company's and ERG's analyses. This means it is less effective but costs less than pembrolizumab alone. The committee considered that, when an ICER is estimated for a technology that is less effective and less costly than its comparator, the commonly assumed decision rule of accepting ICERs below a given threshold is reversed. So, the higher the ICER, the more cost effective a treatment is. The committee noted that the south-west quadrant ICERs were not high enough for pembrolizumab combination therapy to be considered a cost-effective use of NHS resources. The committee noted the cost-effectiveness estimates in this subgroup were not relevant specifically to people with an urgent critical need for a clinical response (see section 3.12). It concluded that, for people with metastatic squamous NSCLC and PD-L1 tumour proportion scores of 50% or more,

pembrolizumab combination therapy could not be considered cost effective.

Other factors

There are no equalities issues, and all relevant benefits are captured in the QALY

3.14 No relevant equalities issues were identified and all relevant benefits of the technology were captured in the QALY.

Conclusion

Pembrolizumab combination therapy is not recommended for routine use in adults with untreated metastatic squamous NSCLC

3.15 After considering its preferred modelling assumptions and NICE's criteria about life-extending treatments at the end of life, the committee concluded that the ICER range for pembrolizumab combination therapy was above what would normally be considered a cost-effective use of NHS resources. The committee agreed that its preferred cost-effectiveness analysis would include the weighted values for PD-L1 tumour proportion scores of less than 50% and PD-L1 tumour proportion scores of 50% or more. It considered that the cost-effectiveness estimates for the PD-L1 subgroup with tumour proportion scores of less than 50% were above what it would normally consider a useful use of NHS resources. The cost-effectiveness estimates for the PD-L1 subgroup with tumour proportion scores of at least 50% were not high enough to be considered a cost-effective use of NHS resources. It also thought that there was considerable unexplored uncertainty in the evidence. Therefore, the committee did not recommend pembrolizumab combination therapy for routine use in adults with untreated metastatic squamous NSCLC.

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.

Gary McVeigh
Chair, appraisal committee
August 2021

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.

Victoria Gillis-Elliott

Technical lead

Christian Griffiths

Technical adviser

Gavin Kenny

Project manager

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