NICE National Institute for Health and Care Excellence

NICE guidance

Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces TA600.

1 Recommendations

1.1 Pembrolizumab with carboplatin and paclitaxel is recommended as an option for untreated metastatic squamous non-small-cell lung cancer (NSCLC) in adults, only if

- their tumours express PD-L1 with a tumour proportion score of 0% to 49%
- their tumours express PD-L1 with a tumour proportion score of 50% or more and they need urgent clinical intervention
- it is stopped at 2 years of uninterrupted treatment or earlier if their disease progresses and
- the company provides pembrolizumab according to the commercial arrangement.

1.2 This recommendation is not intended to affect treatment with pembrolizumab plus carboplatin and paclitaxel that was started in the Cancer Drugs Fund before this guidance was published. For those people, 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 with carboplatin and paclitaxel for untreated metastatic squamous NSCLC.

Initial treatment for metastatic squamous NSCLC depends on PD-L1 tumour proportion score. People whose tumours have a PD-L1 tumour proportion score of 0% to 49%, usually have cisplatin or carboplatin plus either gemcitabine, paclitaxel or vinorelbine (platinum-based combination chemotherapy). People whose tumours have a PD-L1 tumour proportion score of 50% or more usually have pembrolizumab alone.

Clinical trial evidence shows that pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel (pembrolizumab combination therapy) increases how long people with metastatic squamous NSCLC live compared with placebo plus carboplatin and paclitaxel or nab-paclitaxel.

Pembrolizumab combination therapy meets NICE's criteria to be considered a life-extending treatment at the end of life in both PD-L1 tumour proportion score subgroups. The cost-effectiveness estimates in people whose tumours express PD-L1 with a tumour proportion score of 0% to 49% were within what NICE considers a good use of NHS resources. For people whose tumours have a PD-L1 tumour proportion score of 50% or more and who need an urgent clinical intervention (for example, because their cancer may cause major airway blockage), the cost-effectiveness estimates were not certain. However, they are likely to be within what NICE considers a good use of NHS resources, so pembrolizumab combination is recommended in both groups.

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'.

Dosage in the marketing authorisation

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

Price

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

2.4 The company has a commercial arrangement. This makes pembrolizumab available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Merck Sharp and Dohme, 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 with carboplatin and paclitaxel or nab-paclitaxel (from now referred to as 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.

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 more smoking-related comorbidities. For people with squamous NSCLC whose tumours express PD-L1 with a tumour

proportion score of 0% to 49%, 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 for people whose tumours express PD-L1 at 50% or more, most clinicians would use pembrolizumab monotherapy to avoid chemotherapy toxicity. But they added that some people who need urgent clinical intervention (for example, people with impending major airway obstruction) may benefit from initial combination therapy with pembrolizumab and chemotherapy. The committee concluded that pembrolizumab combination therapy would be a welcome additional treatment option for untreated metastatic squamous NSCLC.

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 monotherapy is recommended only for people whose tumours express PD-L1 at 50% or more. At consultation, clinical feedback stated that in clinical practice people would be assessed and treatment decisions would be made based on the 3 PD-L1 tumour proportion scores (that is, PD-L1 tumour proportion scores of less than 1%,1% to 49% and 50% or more). The committee was aware of the different treatment options for people whose tumours express PD-L1 at different levels (see section 3.1). It was satisfied that prognosis may be dependent on the 3 PD-L1 subgroups but that treatment options may not be. It concluded that subgroups based on PD-L1 tumour proportion scores of 0% to 49% and 50% or more should be considered separately.

Clinical management

Pembrolizumab combination therapy should be considered in the same groups that had access in the Cancer Drugs Fund

3.3 Pembrolizumab monotherapy is the standard first-line treatment option for people whose cancer has a PD-L1 tumour proportion score of 50% or more. The company, in its original submission, did an indirect treatment comparison of pembrolizumab combination therapy and pembrolizumab monotherapy using data from KEYNOTE-407 and KEYNOTE-042. KEYNOTE-042 was a trial including 1,274 people with PD-L1-positive tumours that compared pembrolizumab monotherapy with platinum-based chemotherapy. After consultation the company clarified that it was seeking continued access to pembrolizumab combination only for those groups that had access in the Cancer Drugs Fund. That is,

- everyone with a PD-L1 tumour proportion score of 0% to 49% and

- people with a PD-L1 tumour proportion score of 50% or more who need urgent clinical intervention (defined in the Cancer Drugs Fund as people who 'require an urgent clinical response [for example, impending major airway obstruction] so as to justify the use of the combination of pembrolizumab, carboplatin and paclitaxel rather than pembrolizumab monotherapy').

  The company stated the comparator was chemotherapy for people with a PD-L1 tumour proportion score of 50% or more who would benefit from urgent clinical intervention. This was in line with the comparator in KEYNOTE-407. It considered the company's indirect treatment comparison to be no longer relevant. The clinical lead for the Cancer Drugs Fund noted that prescribing data in the Cancer Drugs Fund showed that out of the 1,015 people who received pembrolizumab combination, 113 (11%) had a PD-L1 tumour proportion score of 50% or more and needed urgent clinical intervention. The committee heard that for this group the aim of pembrolizumab combination treatment is for chemotherapy to shrink the tumour, which is compressing the airway, so the person can benefit from pembrolizumab later. The ERG noted that data from KEYNOTE-407 was based on the broader group with PD-L1 tumour proportion scores of 50% or more and did not reflect the company's intended population of those who need urgent clinical intervention. The committee were satisfied that the smaller subgroup was appropriate to consider. Clinical advice suggested that this group did benefit from pembrolizumab combination therapy. The committee concluded pembrolizumab combination therapy should be considered for the same groups that had access in the Cancer Drugs Fund. This includes people with tumours that have a PD-L1 tumour proportion scores of 50% or more who need urgent clinical intervention.

Clinical evidence

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

3.4 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%. At technical engagement, the company provided additional overall-survival data from a later follow up of KEYNOTE-407 (data cut September 2020). Median overall survival was 17.2 months for pembrolizumab combination therapy and 11.6 months for standard chemotherapy (hazard ratio [HR] 0.71, 95% confidence interval [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 PD-L1 tumour proportion score. 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 0% to 49% and 50% or more in those who need urgent clinical intervention).

People in the PD-L1 subgroups would also benefit from pembrolizumab combination therapy

3.5 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 50% or more). The final analysis of KEYNOTE-407 (data cut May 2019) showed a reduction in risk of death of:

- 21% for people with a PD-L1 tumour proportion score of less than 1% (HR 0.79, 95% CI 0.56 to 1.11)
- 41% for people with PD-L1 tumour proportion scores of 1% to 49% (HR 0.59, 95% CI 0.42 to 0.84)
- 21% 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 noted the results suggested pembrolizumab combination therapy was effective at reducing risk of death in people with PD-L1 tumour proportion scores of 1% to 49%. However, it noted that these results were not conclusive. The results for people with PD-L1 tumour proportion scores of less than 1% and 50% or more were less statistically certain. At consultation the company provided additional overall- and progression-free survival data from the September 2020 data cut of KEYNOTE-407. Although the values are academic in confidence and so cannot be reported directly, the company suggested this meant the evidence base is sufficiently robust and mature enough to ensure cost-effectiveness estimates are no longer associated with meaningful uncertainty. The committee noted that the confidence intervals for overall survival crossed 1.0 in the PD-L1 subgroups of less than 1% and for those with PD-L1 scores of at least 50% or more. This suggested that there may not be a difference between pembrolizumab combination therapy and standard care in these groups. The results showed that 26.6% of those having pembrolizumab combination therapy were still alive at the September 2020 data cut from KEYNOTE-407, and 18.1% of those having standard chemotherapy had survived without their cancer progressing. The committee concluded that people in the PD-L1 subgroups would also benefit from pembrolizumab combination therapy.

The company's economic model

The company's updated economic model is appropriate

3.6 The company's economic analysis was based on 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 May 2019 data cut of KEYNOTE-407 and updated to the September 2020 cut after consultation:

- 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 included 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.

  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 enough for decision making.

The 0% to 49% PD-L1 subgroup should be weighted by the Cancer Drug Fund usage

3.7 The committee recalled that its preference was to consider the PD-L1 subgroups based on those with tumour proportion scores of 0% to 49% and those with 50% or more who need urgent clinical intervention (see section 3.2 and section 3.3). After consultation the company agreed this

was appropriate. The committee was aware that because the KEYNOTE-407 trial did not include a prespecified subgroup of people whose tumours express PD-L1 at less than 50%, there was no evidence on the effectiveness of pembrolizumab combination therapy in this group. Therefore, the ERG weighted the life years gained, quality-adjusted life years (QALYs) and costs from the company's model with the proportions from the KEYNOTE-407 groups with PD-L1 expression of less than 1% and 1% to 49%. After the first committee meeting, the company noted that recent prescribing data had identified differences in the proportions using pembrolizumab combination therapy in the trial compared with those in NHS clinical practice. It suggested that the market research prescribing data was the most accurate source to weight the 0% to 49% PD-L1 subgroup. This showed that pembrolizumab combination therapy was used in NHS clinical practice by 22% of those with PD-L1 tumour proportion scores of less than 1% and 68% of those with tumour proportion scores of 1% to 49%. In KEYNOTE-40, 35.5% of patients receiving pembrolizumab combination therapy had a PD-L1 tumour proportion scores less than 1% and 37.8% had tumour proportion scores of 1% to 49%. At the second committee meeting the clinical lead for the Cancer Drugs Fund explained that 48% of those with PD-L1 tumour proportion scores of less than 1% and 41% of those with tumour proportion scores of 1% to 49% had accessed pembrolizumab combination therapy in the Cancer Drugs Fund. The committee considered the 3 data sources and agreed that the Cancer Drugs Fund was the most accurate source of prescribing data because it was based upon real-world use of pembrolizumab combination therapy. This data showed the total number of people who had received treatment with pembrolizumab combination therapy for metastatic squamous NSCLC in the NHS. It concluded the Cancer Drugs Fund prescribing data is the most appropriate source to weight the 0% to 49% PD-L1 subgroup.

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

3.8 In the original appraisal, the company and the ERG used various modelling approaches to estimate long-term survival in 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 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 progression-free survival, the company fitted the same hybrid model it used in the original appraisal, updated with the May 2019 data cut off. At the first committee meeting 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 initially 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. After consultation the company updated its economic model for the 3 PD-L1 subgroups. It used the September 2020 data cut from KEYNOTE-407, justifying its choice of extrapolation model for the PD-L1 subgroups with

tumour proportion scores of less than 1%, 1% to 49%, and 50% or more based on goodness-of-fit assessments. The ERG noted that the company's consultation response had not considered the plausibility of the chosen model. However, at the second committee meeting, the company clarified that the clinical plausibility of the extrapolation models had been considered in its original submission during the committee's decision making for NICE's original technology appraisal for pembrolizumab combination therapy with carboplatin and paclitaxel for untreated metastatic squamous NSCLC. The committee concluded the company's choice of parametric models to extrapolate overall and progression-free survival was appropriate for decision making.

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

3.9 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. At consultation, the company recognised there were problems with each approach taken. It considered that using KEYNOTE-407 data on subsequent treatments might undervalue the cost-effectiveness of pembrolizumab combination therapy. But, it stated, it would accept using the 'within-trial' approach adopted by the ERG. The committee agreed

that the costs of subsequent treatment included in the economic model should reflect the treatments in KEYNOTE-407.

A treatment effect lasting 5 years for both overall and progression-free survival is appropriate for decision making

3.10 In the original appraisal, the committee's preferred analysis included a 2-year treatment stopping rule and a treatment effect lasting between 3 years and 5 years. 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. At its first meeting, the committee considered the company's and ERG's preferred assumptions alongside decisions made in previous appraisals of immunotherapies and agreed there was no new evidence presented to change its position from the original appraisal. So, it concluded that, for consistency with previous appraisals of immunotherapies for NSCLC, a treatment effect lasting between 3 years and 5 years after starting treatment was appropriate for decision making. In its response to consultation, the company stated its new data cut from September 2020 of KEYNOTE-407, showing a follow up beyond 3 years did not support the committee's preference on waning of treatment effect. The company updated its economic analyses to include a treatment effect for overall survival up to 5 years but assumed a lifetime treatment effect for progression-free survival. The ERG noted the Kaplan–Meier data from the September 2020 data cut -off of KEYNOTE-407 and suggested there may be high levels of censoring and both treatment groups had few overall-survival events at later

time points. The data did not show whether the treatment effect would continue for longer than 4 years. Although alternative analyses such as using empirical hazard functions and log cumulative hazards may have assessed whether the treatment effects persisted longer term, these had not been used. The committee agreed the longer-term data of KEYNOTE-407 showed the treatment effect of pembrolizumab combination therapy probably did not wane before 4 years. It was satisfied with the company's assumption for overall survival but it was unclear about the company's rationale about whether the treatment effect for progression-free survival would persist for a lifetime duration. It considered that treatment waning is usually an assumption that is applied when the available data is immature, and so cannot show what happens when people stop having treatment. However, it had agreed the KEYNOTE-407 was now more mature and it was reasonable to assume that the treatment effect for progression-free survival would follow a similar trajectory to overall survival. For this reason the committee concluded that a treatment effect lasting 5 years for both overall and progression-free survival is appropriate for decision making.

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

3.11 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 did not fit 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 model 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 both PD-L1 subgroups

3.12 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 benefit of 5.6 months with pembrolizumab combination therapy compared with standard care. However, the survival benefit based on the May 2019 data cut of KEYNOTE-407 was more uncertain for 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). At the second committee meeting the committee considered the new evidence on the PD-L1 subgroups provided by the company from the September 2020 data cut of KEYNOTE-407. The committee agreed, there was a clinical unmet need for people in the 50% or more PD-L1 subgroup, who have additional complications that require an urgent clinical response. By definition, this group would need urgent clinical intervention and would likely be particularly unwell. They would therefore need a treatment that would prolong their life, which is likely to exceed 3 months. For people in the 0% to 49% PD-L1 subgroup, the committee noted that using the company's latest model with the Cancer Drug Fund prescribing data to inform the weighting, suggested an extension to life of at least 3 months. It concluded that pembrolizumab combination therapy would likely meet the extension-to-life criterion for people with a PD-L1 tumour proportion score of 0% to 49% and for those with a PD-L1 tumour proportion score of 50% or more who need urgent clinical intervention.

The short-life-expectancy criterion is likely met

3.13 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. 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 company noted that survival with current therapies in NICE's ongoing technology

appraisal for nivolumab with ipilimumab and chemotherapy for untreated metastatic NSCLC 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. At the second committee meeting, the company accepted that NICE's end of life criteria should be considered based on the PD-L1 subgroups of 0% to 49% and 50% or more in those who need urgent clinical intervention. The committee noted that the company's updated base case using the September 2020 data cut and weighted using the percentage usage from the Cancer Drugs Fund, suggested that people on standard chemotherapy would live approximately 2 years. It concluded that the short-life-expectancy criterion was likely met for both subgroups.

Cost-effectiveness estimates

An acceptable ICER is £50,000 per QALY gained

3.14 NICE's guide to the methods of technology appraisal notes that above a most plausible ICER of £20,000 per 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'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 treatment effect for both overall and progression-free survival lasting 5 years after starting treatment
- weighting the cost-effectiveness results of the less than 1% and 1% to 49% PD-L1 subgroups using the Cancer Drugs Fund prescribing data.

The committee considered its conclusion that the end of life criteria is likely met for both PD-L1 subgroups (see section 3.12 and section 3.13). Therefore, it agreed that an acceptable ICER would be £50,000 per QALY gained.

Pembrolizumab combination is recommended for routine use in the 0% to 49% PD-L1 subgroup

3.15 The committee considered the results of its preferred analysis for the 0% to 49% PD-L1 subgroup, reweighted using the prescribing data from the Cancer Drugs Fund. The ICER was below £50,000 per QALY gained. The committee concluded that pembrolizumab combination is recommended for routine use in people whose tumours express PD-L1 with a tumour proportion score of 0% to 49%.

Pembrolizumab combination is recommended for routine use in the 50% or more PD-L1 subgroup who need urgent clinical intervention

3.16 The committee considered the results of its preferred analysis for the 50% or more PD-L1 subgroup who need urgent clinical intervention. The ICER was below £50,00 per QALY gained. It noted it had not seen any direct or indirect evidence specifically for the 50% or more PD-L1 subgroup who need urgent clinical intervention. It considered there was a high unmet need for this group because there is a lack of other treatment options available and because this group are likely to have a very short life expectancies. It considered the ICER was likely to be a cost-effective use of NHS resources, despite the lack of a robust evidence in the subgroup. For this reason, the committee concluded that pembrolizumab combination therapy is recommended for routine use in the NHS for people whose tumours have a PD-L1 tumour proportion score of 50% or more and who need urgent clinical intervention.

Other factors

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

3.17 At consultation, the company highlighted that people with squamous NSCLC could have poorer outcomes because of smoking-related comorbidities. It suggested this was likely to have an impact on people in lower socioeconomic groups because rates of smoking are higher in these populations. The committee noted it had no evidence to suggest outcomes would differ for this group of people compared with people who had other cancers. The committee concluded there are no equalities issues and all relevant benefits of the technology were captured in the QALY.

4 Implementation

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

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. 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 squamous non-small-cell lung cancer and the doctor responsible for their care thinks that pembrolizumab combination therapy is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal committee members and NICE project team

Appraisal committee members

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

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Accreditation