

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 are 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.

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.

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1 Recommendations

- 1.1 Pembrolizumab, with carboplatin and paclitaxel, is recommended for use within the Cancer Drugs Fund as an option for untreated metastatic squamous non-small-cell lung cancer (NSCLC) in adults only if:
- pembrolizumab is stopped at 2 years of uninterrupted treatment, or earlier if disease progresses, and
 - the company provides pembrolizumab according to the [managed access agreement](#).
- 1.2 This recommendation is not intended to affect treatment with pembrolizumab, with carboplatin and paclitaxel, 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

Current treatment for untreated metastatic squamous NSCLC is usually platinum-based combination chemotherapy (standard chemotherapy) for people whose tumours express PD-L1 with a tumour proportion score of lower than 50%, or pembrolizumab monotherapy for people whose tumours express PD-L1 with a tumour proportion score of 50% or higher.

The main clinical evidence for pembrolizumab with carboplatin and paclitaxel (pembrolizumab combination therapy) comes from an ongoing randomised controlled trial (KEYNOTE-407). This suggests that people who have pembrolizumab combination therapy live longer than those who have standard chemotherapy. Pembrolizumab combination therapy has only been indirectly compared with pembrolizumab monotherapy in people whose tumours express PD-L1 with a tumour proportion score of 50% or higher.

Because the clinical evidence is immature, the cost-effectiveness estimates for pembrolizumab combination therapy are very uncertain. It may meet NICE's criteria to be considered a life-extending treatment at the end of life when compared with standard chemotherapy, but there is uncertainty about this. It does not meet the end-of-life criteria when compared with pembrolizumab monotherapy for people whose tumours express PD-L1 with a tumour proportion score of 50% or higher. Pembrolizumab should be stopped at 2 years of uninterrupted treatment or earlier if disease progresses because the clinical- and cost-effectiveness evidence is limited to

2 years of treatment and the best treatment duration is unknown.

Pembrolizumab combination therapy has the potential to be cost effective, but more evidence is needed to address the clinical uncertainties. Therefore, it is recommended for use in the Cancer Drugs Fund for untreated metastatic squamous NSCLC in adults.

2 Information about pembrolizumab with carboplatin and paclitaxel

Marketing authorisation indication	Pembrolizumab (Keytruda, Merck Sharp & Dohme), 'in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous NSCLC in adults'.
Dosage in the marketing authorisation	200 mg every 3 weeks by intravenous infusion (when part of combination therapy). The summary of product characteristics recommends treatment with pembrolizumab until disease progression or unacceptable toxicity.
Price	£2,630 per 100-mg/4-ml vial (BNF online, accessed April 2019). 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 ([section 5](#)) considered evidence submitted by Merck Sharp & Dohme, a review of this submission by the evidence review group (ERG), and the technical report developed through engagement with stakeholders. See the [committee papers](#) for full details of the evidence.

The appraisal committee was aware that several issues were resolved during the technical engagement stage (see the final technical report, page 40, table 4), and agreed that:

- Pembrolizumab with carboplatin and paclitaxel (pembrolizumab combination therapy), if approved by NICE, would be a treatment option for people with untreated squamous non-small-cell lung cancer (NSCLC).
- All standard chemotherapy regimens for treating squamous NSCLC can be considered equal in terms of efficacy. Therefore, the company's indirect treatment comparison is not needed for the subgroup whose PD-L1 tumour proportion score is lower than 50% even though the comparator included in the pivotal trial (KEYNOTE-407) was not the same treatment as that included in the final NICE scope. An indirect treatment comparison between pembrolizumab combination therapy and pembrolizumab monotherapy is needed for the subgroup whose PD-L1 tumour proportion score is 50% or higher. This is because pembrolizumab monotherapy was not included as a comparator in the pivotal trial but is standard care in the NHS for treating tumours expressing PD-L1 at 50% or higher. The company's indirect treatment comparison used data from the KEYNOTE-407 and KEYNOTE-042 clinical trials. KEYNOTE-042 compared pembrolizumab monotherapy with standard chemotherapy in people with untreated metastatic NSCLC.

The committee recognised that there were remaining areas of uncertainty associated with the analyses presented and took these into account in its decision making. It discussed issues 1, 3, 4, 6, 7, 8 and 9 in the final technical report, which were outstanding after the technical engagement stage.

Clinical need

There is an unmet need for treatment options in this disease area

- 3.1 Patient experts explained that people with squamous NSCLC often have a poor quality of life, and that potential extension to life is of great importance. There is currently an unmet need in this population. Outcomes tend to be worse for people with squamous NSCLC because they have a higher prevalence of

smoking-related comorbidities than people with non-squamous NSCLC. For people whose tumours express PD-L1 with a tumour proportion score lower than 50%, outcomes are particularly poor because treatment for untreated disease is currently standard chemotherapy. Pembrolizumab monotherapy for people whose tumours express PD-L1 with a tumour proportion score of 50% or higher has been a welcomed recent treatment option. The committee heard from the clinical experts that, while most clinicians would use pembrolizumab monotherapy for people whose tumours express PD-L1 at 50% or higher to avoid the additional toxicity of chemotherapy, a few people who need an urgent, rapid response may benefit from initial combination therapy with pembrolizumab and chemotherapy (for example, those with bulky central disease). Clinical experts commented that the role of biomarkers, such as PD-L1, to predict which cancers are most likely to respond to immunotherapy, is less well established in squamous NSCLC than in non-squamous NSCLC. The committee agreed that an additional treatment option would benefit people with untreated, squamous NSCLC and concluded that pembrolizumab combination therapy would be a welcome additional treatment option.

Clinical evidence

KEYNOTE-407 does not include all the relevant treatments used in NHS clinical practice

- 3.2 The clinical evidence for pembrolizumab combination therapy came from KEYNOTE-407, an ongoing, randomised placebo-controlled trial. This trial compares pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel with placebo plus carboplatin and paclitaxel or nab-paclitaxel in adults with untreated advanced or metastatic squamous NSCLC with an Eastern Cooperative Oncology Group performance status of 0 or 1. In NHS clinical practice, carboplatin plus gemcitabine is the most commonly used chemotherapy regimen for people whose tumours express PD-L1 with a tumour proportion score of lower than 50%. Nab-paclitaxel is not commissioned by NHS England. During technical engagement, it was concluded that all standard chemotherapy treatments can be considered to be of equal efficacy, and therefore KEYNOTE-407 was relevant for decision making for this population. KEYNOTE-407 did not include the comparator treatment used in NHS clinical practice for the PD-L1 tumour proportion score of 50% or higher subgroup (that is, pembrolizumab monotherapy). The committee acknowledged that, because

there was no head-to-head evidence with the relevant comparator for this subgroup, an indirect treatment comparison was needed to assess the effectiveness of pembrolizumab combination therapy compared with pembrolizumab monotherapy. The committee concluded that KEYNOTE-407 only directly provided evidence relevant to the subgroup of people whose tumours express PD-L1 with a tumour proportion score of lower than 50%.

Pembrolizumab combination therapy improves overall and progression-free survival compared with standard chemotherapy but by how much is unclear

3.3 An interim analysis of KEYNOTE-407 showed a statistically significant difference in overall and progression-free survival in favour of pembrolizumab combination therapy compared with standard chemotherapy. At the most recent data-cut (April 2018), median overall survival was 15.9 months for pembrolizumab combination therapy and 11.3 months for standard chemotherapy (hazard ratio [HR] 0.64, 95% confidence interval [CI] 0.49 to 0.85). Median progression-free survival was 6.4 months for pembrolizumab combination therapy and 4.8 months for standard chemotherapy (HR 0.56, 95% CI 0.45 to 0.70). However, median overall survival was not reached in KEYNOTE-407 for the PD-L1 tumour proportion score of 50% or higher subgroup in either arm. The committee acknowledged that the KEYNOTE-407 data were very immature (median follow-up of 7.8 months) and that this meant there was substantial uncertainty about the size of the benefit. It concluded that treatment with pembrolizumab combination therapy lengthened overall and progression-free survival compared with standard chemotherapy, but that survival benefit was uncertain because the data were very immature.

Indirect treatment comparison

The indirect treatment comparison between pembrolizumab combination therapy and pembrolizumab monotherapy is not adequate for decision making

3.4 Because KEYNOTE-407 does not include the comparator treatment used in NHS clinical practice for the PD-L1 tumour proportion score of 50% or higher subgroup, the company has done an indirect treatment comparison to compare pembrolizumab combination therapy with pembrolizumab monotherapy. To inform the clinical effectiveness of pembrolizumab monotherapy, data from KEYNOTE-407 and KEYNOTE-042 were used. The indirect treatment

comparison was done using the Bucher method after adjustments to the population and treatment arms, and assuming proportional hazards. The hazard ratio for the comparison was 0.97 (95% CI 0.50 to 1.89). There was considerable uncertainty about the source used for the time to treatment discontinuation for pembrolizumab monotherapy, and it was not considered a valid estimate. Given the post-hoc nature of the subgroup analyses, uncertainties relating to the potential heterogeneity between studies and the time on treatment for pembrolizumab monotherapy, the committee concluded that the outputs from the indirect treatment comparison were not robust enough for decision making.

Clinical evidence in the economic model

The subgroup analysis is not robust enough for decision making

3.5 The committee considered the subgroup analysis because treatment options differ by PD-L1 tumour proportion score. People whose tumours express PD-L1 with a tumour proportion score of lower than 50% are offered standard chemotherapy and those whose tumours express PD-L1 with a tumour proportion score of 50% or higher are offered pembrolizumab monotherapy in NHS clinical practice. The ERG explained that the subgroup analysis should be considered exploratory. This was because specific PD-L1 subgroup Kaplan–Meier curves (tumour proportion score less than 1%, 1% to 49%, and 50% or higher) from KEYNOTE-407 were used, with the same extrapolation method applied to estimate overall survival as for the intention-to-treat population. These extrapolations may not be the most appropriate for subgroup analyses. In addition, the ERG's clinical advisers could not give survival estimates by PD-L1 tumour proportion score because it was too uncertain. The committee concluded that decisions should be made using data from the full intention-to-treat population because the subgroup analysis was not considered robust enough for decision making.

Modelling of overall survival

The ERG model, which uses a log-logistic model with no cut point for both treatment arms, is more appropriate for decision making

3.6 Various modelling approaches were done by the company and the ERG to estimate long-term survival in both the pembrolizumab combination therapy and the comparator arms. The company's modelling used external data from the

US Surveillance, Epidemiology and End Results (SEER) database for extrapolating overall survival in both treatment arms, with a relative risk (from month 7 to month 12 in KEYNOTE-407) applied indefinitely in the pembrolizumab combination arm. One ERG model used the SEER database to extrapolate overall survival in the standard chemotherapy arm, with a log-logistic extrapolation using a 19-week cut point in the pembrolizumab combination therapy arm. The clinical experts agreed that the SEER database is not appropriate for decision making because it does not include second-line immunotherapy treatments. The company's use of a relative risk function from month 7 to month 12, and applied indefinitely, in the extrapolation of overall survival in the pembrolizumab combination therapy arm was also not appropriate because risks would be expected to change over time. In addition, the company's modelled overall survival in the pembrolizumab combination arm was considered too optimistic by all clinical experts; the ERG's modelled estimates were deemed more plausible. The committee concluded that it preferred the ERG's model, which did not use the SEER database or piecewise modelling and instead applied a log-logistic extrapolation in each treatment arm with no cut points.

Duration of treatment benefit after progression

A lifetime treatment effect is not plausible and the company's cure estimate is too optimistic

3.7 The company's lifetime treatment effect for pembrolizumab combination therapy was not considered to be plausible because there was no evidence to suggest this duration of benefit. The committee also noted that a lifetime treatment effect was deemed implausible in previous NICE technology appraisals of immunotherapies in NSCLC, and that a treatment effect lasting between 3 years and 5 years had been considered more appropriate for those with a 2-year stopping rule. The company's modelling approach also assumed that about 10% of people having pembrolizumab combination therapy would be cured after 18 years. The clinical experts explained that such a cure rate would be optimistic given the increased risk of secondary cancers and the other comorbidities in this population. The committee concluded that a lifetime treatment effect was implausible, and that the company's cure estimate was too optimistic.

The ERG's model using the log-logistic extrapolation in both arms captures the treatment effect in the intervention arm most adequately

3.8 The clinical experts agreed that the company's modelling approach resulted in unreasonably high survival in the pembrolizumab combination therapy arm. The ERG's fully parametric log-logistic model with no cut points provided survival estimates that were in a range supported by clinical opinion. Therefore, it was decided that this model most adequately estimated the treatment benefits of pembrolizumab combination therapy. This ERG model did not include an explicit treatment effect but did include a varying hazard ratio over time because the parametric extrapolations were chosen to match their clinical adviser estimates. The committee concluded that the ERG's model, using the log-logistic extrapolation in both arms, most adequately captured treatment effect in the intervention arm.

Stopping rule

Including a stopping rule is acceptable

3.9 The company included a 2-year treatment stopping rule in its model. The committee was aware that the maximum possible treatment duration with pembrolizumab combination therapy in KEYNOTE-407 was 35 cycles (that is, 2 years of treatment). It noted that, despite this, the summary of product characteristics states that treatment should continue until disease progression or unacceptable toxicity. The committee noted that implementing a 2-year stopping rule was consistent with other NICE technology appraisal guidance on untreated NSCLC ([TA531](#) and [TA557](#)). The committee understood that, in clinical practice, people would be able to have treatment breaks to recover from any toxicities associated with pembrolizumab combination therapy and that this would not be considered as interrupted treatment. The committee concluded that a 2-year treatment stopping rule in line with the clinical- and cost-effectiveness evidence was acceptable.

Subsequent treatments

The economic models do not capture the benefits of subsequent treatments appropriately

3.10 In UK clinical practice, people who have had treatment with standard

chemotherapy could be offered an immunotherapy (pembrolizumab or atezolizumab) after disease progression. Following clinical expert opinion, it was assumed that around 50% of people would have immunotherapy after disease progression, which was higher than the proportion seen in KEYNOTE-407. The committee noted that, although the costs of second-line treatments were applied in the standard care arm of the model, the benefits were not captured. Therefore, increasing the proportion of second-line immunotherapy in the company and ERG models to reflect NHS clinical practice only increased costs for the standard care arm. The incremental cost-effectiveness ratios (ICERs) decreased because health benefits were not captured. The committee accepted that, in NHS clinical practice, a higher proportion of people would have subsequent treatment with an immunotherapy. It concluded that the benefits of these treatments were not appropriately captured in the economic models.

The distribution of subsequent treatments in the economic model does not reflect current NHS clinical practice

3.11 In the company and ERG models, the proportions of second-line immunotherapies in the standard care arm were 65% for pembrolizumab and 35% for atezolizumab. The Cancer Drugs Fund clinical lead explained that, in current NHS practice, for people whose tumours express PD-L1 with a tumour proportion score lower than 50% and who are fit enough for second-line treatment with an immunotherapy, atezolizumab is given more often than pembrolizumab (about 75% and 25% respectively). The ERG provided an additional analysis on the distribution of subsequent treatments, which included the proportions of second-line atezolizumab and pembrolizumab as estimated by the Cancer Drugs Fund clinical lead. The committee accepted the ERG's additional analysis and concluded that the distribution of subsequent treatments in the company's model did not reflect current NHS clinical practice.

Health-related quality of life

The ERG's approach of using progression-based utility values is preferred

3.12 The ERG explained that the company's time-to-death approach was not appropriate. This was because the utility values for the 2 least severe health states (more than 360 days to death and between 180 and 360 days to death) were similar to those of the general public, adjusted for age, which the ERG did not consider clinically plausible. The ERG used a progression-based approach,

which included the pre-progression utility value from KEYNOTE-407 and a post-progression value (0.58) from the TOPICAL trial (Khan et al. 2014). This trial included EQ-5D assessments for patients whose cancer had progressed, and low numbers in the placebo group had active therapy after progression. The committee preferred this approach because it addressed the issue of informative censoring (because EQ-5D assessments for people whose disease progressed were done only shortly after disease progression) for the progressed population in KEYNOTE-407. The committee agreed that the post-progression utility value from Khan et al. was the most appropriate because it had previously accepted this post-progression utility value (although from a different source). It concluded that the ERG's approach of using progression-based utility values was appropriate for decision making.

Cost-effectiveness estimate

The most plausible ICER for pembrolizumab combination therapy is highly uncertain

3.13 The committee recalled its preferred modelling assumptions, which were:

- log-logistic extrapolation, with no cut points, to estimate long-term survival for both the standard chemotherapy and pembrolizumab combination arms (see [section 3.6](#))
- progression-based utilities with a pre-progression utility from KEYNOTE-407 and a post-progression utility from TOPICAL (Khan et al. 2014; see [section 3.12](#))
- the assumption that around 50% of people in the standard care arm would be offered subsequent treatments (of these, 75% would have atezolizumab and 25% would have pembrolizumab in NHS clinical practice; see [sections 3.10](#) and [3.11](#)).

Using the above assumptions, the ICER (recalculated by the ERG to include the confidential commercial arrangements for pembrolizumab and subsequent treatments) was higher than £50,000 per quality-adjusted life year (QALY) gained. However, the ICER was considered highly uncertain. This was because of the short duration of interim KEYNOTE-407 data and concerns that subsequent treatment benefits in the standard chemotherapy arm were not adequately captured in the modelling. The committee concluded that the most plausible ICER was above £50,000 per QALY gained but considered this estimate to be highly uncertain.

End of life

Pembrolizumab combination therapy may meet NICE's end-of-life criteria but there is uncertainty about life expectancy in the standard care arm

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](#). Based on evidence from KEYNOTE-407 and predictions from the economic model (using the committee's preferred assumptions), the committee concluded that pembrolizumab combination therapy was likely to extend life by over 3 months, so the extension-to-life criterion was met. The preferred ERG economic model predicted a mean survival of 2.17 years in the standard care arm. It was noted that, because the interim trial data were of very short duration, the modelled estimates were based on very immature data. The clinical experts stated that life expectancy for the intention-to-treat population would be under 24 months, even when accounting for the higher life expectancy (over 24 months) for people whose tumours express a PD-L1 tumour proportion score of 50% or higher. Clinical experts explained that squamous NSCLC populations tend to have a poorer prognosis than those with non-squamous NSCLC. The committee acknowledged that there was considerable uncertainty surrounding life expectancy in the standard care arm and that this should be taken into consideration in its decision making. Taking account of the clinical expert opinion, the committee concluded that, on balance, NICE's end-of-life criteria may be met.

Other factors

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

3.15 No relevant equalities issues were identified. Pembrolizumab combination therapy may be innovative. However, all relevant benefits of the technology were captured in the QALY.

Conclusion

Pembrolizumab combination therapy is not recommended for routine use in the NHS

3.16 The long-term overall survival benefit with pembrolizumab combination

therapy was uncertain because of the very short duration of the interim data from KEYNOTE-407. This resulted in uncertain estimates for overall survival for pembrolizumab combination therapy compared with standard chemotherapy. After considering its preferred modelling assumptions and NICE's criteria on end of life, the committee decided that the ICER was not within the range usually considered a cost-effective use of resources. The committee concluded not to recommend pembrolizumab combination therapy for routine use in adults with untreated metastatic squamous NSCLC.

Pembrolizumab combination therapy is recommended for use in the Cancer Drugs Fund

3.17 Having concluded that pembrolizumab combination therapy could not be recommended for routine use, the committee then considered whether it could be recommended within the Cancer Drugs Fund. 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 committee was aware that the company had expressed an interest in the treatment being considered for funding through the Cancer Drugs Fund. It was also aware that KEYNOTE-407 was ongoing, and more data would be available. It agreed that:

- Further data on overall survival would inform decisions on the effectiveness of pembrolizumab combination therapy compared with standard care for the intention-to-treat population and by PD-L1 tumour proportion score subgroup.
- Further data on overall survival in the comparator arm, particularly subsequent immunotherapy benefits, would inform decisions about whether NICE's end-of-life criteria have been met.

The committee recalled its conclusion that the current cost-effectiveness results were very uncertain. It agreed that, with longer follow-up data from KEYNOTE-407 on overall survival, pembrolizumab combination therapy has the potential to be cost effective. The committee concluded that pembrolizumab combination therapy met the criteria to be considered for inclusion in the Cancer Drugs Fund. It recommended pembrolizumab combination therapy for use within the Cancer Drugs Fund as an option for people with untreated metastatic squamous NSCLC if the conditions in the managed access agreement are followed.

4 Implementation

- 4.1 When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a patient has untreated metastatic squamous non-small-cell lung cancer (NSCLC) and the doctor responsible for their care thinks that pembrolizumab with carboplatin and paclitaxel is the right treatment, it should be available for use, in line with NICE's recommendations and the Cancer Drugs Fund criteria in the managed access agreement. Further information can be found in NHS England's [Appraisal and funding of cancer drugs from July 2016 \(including the new Cancer Drugs Fund\) – a new deal for patients, taxpayers and industry](#).
- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance when the drug or treatment, or other technology, is approved for use within the Cancer Drugs Fund. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, for use within the Cancer Drugs Fund, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document or agreement of a managed access agreement by the NHS in Wales, whichever is the later.

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

