Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-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 pemetrexed and platinum chemotherapy is recommended for use within the Cancer Drugs Fund, as an option for untreated, metastatic, non-squamous non-small-cell lung cancer (NSCLC) in adults whose tumours have no epidermal growth factor receptor (EGFR)- or anaplastic lymphoma kinase (ALK)-positive mutations. It is only recommended 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 pemetrexed and platinum chemotherapy 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

Standard care in people with untreated, metastatic non-squamous NSCLC whose tumours have no EGFR- or ALK-positive mutations is usually pemetrexed with carboplatin or cisplatin. For people who cannot tolerate this, docetaxel, gemcitabine, paclitaxel or vinorelbine with carboplatin or cisplatin can be offered. People on either of these combinations may also have pemetrexed maintenance therapy. Standard care for people whose tumours express at least a 50% tumour proportion score is usually pembrolizumab monotherapy.

Clinical-effectiveness evidence comes from an ongoing trial (KEYNOTE-189). Pembrolizumab with pemetrexed and carboplatin or cisplatin (pembrolizumab combination) is likely to improve how long people live but it is difficult to establish the size of the benefit in the long term, because the trial is ongoing. Therefore, the cost-effectiveness estimates are also very uncertain.

Pembrolizumab combination meets NICE’s criteria to be considered a life-extending end-of-life treatment compared with standard care and chemotherapy but does not meet the criteria when compared with pembrolizumab monotherapy. Pembrolizumab combination has the potential to be
cost effective, but more evidence from the trial is needed to address the clinical uncertainties. Therefore, pembrolizumab combination is recommended for use in the Cancer Drugs Fund for adults who have untreated, metastatic, non-squamous NSCLC whose tumours have no EGFR- or ALK-positive mutations.

Pembrolizumab should be stopped at 2 years of uninterrupted treatment or earlier if disease progresses because the clinical- and cost-effectiveness evidence was limited to 2 years of treatment and the best duration of treatment is unknown.
### 2 Information about pembrolizumab combination

<table>
<thead>
<tr>
<th>Market authorisation indication</th>
<th>Pembrolizumab (Keytruda, Merck, Sharp &amp; Dohme), plus pemetrexed and carboplatin or cisplatin has a marketing authorisation for 'the first-line treatment of metastatic non-squamous non-small-cell lung carcinoma (NSCLC) in adults whose tumours have no epidermal growth factor receptor or anaplastic lymphoma kinase-positive tumour mutations'.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage in the marketing authorisation</td>
<td>200 mg every 3 weeks by intravenous infusion. The summary of product characteristics recommends treatment with pembrolizumab until disease progression or unacceptable toxicity.</td>
</tr>
<tr>
<td>Price</td>
<td>£1,315.00 per 50 mg vial (excluding VAT; British national formulary online, accessed October 2018). 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.</td>
</tr>
</tbody>
</table>
3 Committee discussion

The appraisal committee (section 6) considered evidence submitted by Merck, Sharp & Dohme and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Clinical management

Pembrolizumab with pemetrexed and carboplatin or cisplatin is an important treatment option for untreated, metastatic, non-squamous non-small-cell lung cancer

3.1 The patient experts explained that symptoms of untreated, metastatic, non-squamous non-small-cell lung cancer (NSCLC) can be debilitating, so improving quality of life and even small extensions in length of life are important. The clinical experts explained that people with untreated, metastatic, non-squamous NSCLC have limited treatment options. NICE’s technology appraisal guidance recommends pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer. The committee understood that for patients whose tumours express a tumour proportion score of less than 50%, treatments can last for a long time and this can cause unpleasant side effects. The clinical experts explained that managing disease in people having pembrolizumab with pemetrexed and platinum chemotherapy (carboplatin or cisplatin), referred to as pembrolizumab combination, should not be substantially different to people having pembrolizumab monotherapy. The committee concluded that pembrolizumab combination is an important treatment option for people with untreated, metastatic, non-squamous NSCLC.

Pembrolizumab combination is an alternative to pemetrexed with carboplatin or cisplatin, chemotherapy with carboplatin or cisplatin and pembrolizumab monotherapy

3.2 Management of untreated, metastatic, non-squamous NSCLC in people whose tumours are not EGFR- or ALK-positive includes pemetrexed with carboplatin or cisplatin, with or without pemetrexed maintenance therapy. NICE’s clinical guideline on lung cancer: diagnosis and management recommends docetaxel,
gemcitabine, paclitaxel or vinorelbine with carboplatin or cisplatin (with or without pemetrexed maintenance therapy) for people who cannot tolerate combination therapy. However, their use in clinical practice is limited. NICE’s technology appraisal guidance on pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer recommends pembrolizumab monotherapy for people whose tumours express at least a 50% tumour proportion score. The clinical experts explained that since publication of this guidance, the use of pembrolizumab monotherapy has become standard care for people whose tumours express at least a 50% tumour proportion score and PD-L1 testing at diagnosis has become routine within the NHS. The committee concluded that pembrolizumab combination would be considered as an alternative to:

- pemetrexed with carboplatin or cisplatin, with or without pemetrexed maintenance therapy
- chemotherapy (that is, docetaxel, gemcitabine, paclitaxel or vinorelbine as monotherapy), with carboplatin or cisplatin, with or without pemetrexed maintenance therapy
- pembrolizumab monotherapy (only in PD-L1-positive NSCLC if the tumour expresses at least a 50% tumour proportion score).

Clinical evidence

KEYNOTE-189 does not include all the relevant treatments used in NHS clinical practice

3.3 The clinical-effectiveness evidence for pembrolizumab combination followed by pemetrexed maintenance therapy compared with standard care came from KEYNOTE-189. This is an ongoing randomised phase 3 trial. Standard care was defined as pemetrexed and placebo, with carboplatin or cisplatin followed by placebo and pemetrexed maintenance therapy. The committee was aware that KEYNOTE-189 included adults with untreated advanced or metastatic NSCLC (with tumours expressing no EGFR- or ALK-positive mutations) with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The trial included all patients regardless of PD-L1 status however, in the pembrolizumab combination group, 63.4% of patients were PD-L1-positive, with a tumour proportion score greater than 1% and in the standard care arm it was 62.1%.
The committee was aware that for people whose tumours express PD-L1 with at least a 50% tumour proportion score, pembrolizumab monotherapy is the preferred treatment in NHS clinical practice. The committee therefore concluded that KEYNOTE-189 was only relevant to people who would have pemetrexed with carboplatin or cisplatin in clinical practice.

**Pembrolizumab combination improves overall survival compared with pemetrexed plus carboplatin or cisplatin, but the size of the benefit in the long term is unclear**

3.4 At the most recent data cut (November 2017), median overall survival for pembrolizumab combination was not reached. The median follow-up was 10.5 months (0.2 to 20.4 months).

### Table 1 Clinical data from KEYNOTE-189

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab combination</th>
<th>Standard care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>410</td>
<td>206</td>
</tr>
<tr>
<td>ITT OS, median (95% CI)</td>
<td>Not reached</td>
<td>11.3 (8.7 to 15.1)</td>
</tr>
<tr>
<td>ITT OS at 12 months</td>
<td>69.2%</td>
<td>49.4%</td>
</tr>
<tr>
<td>ITT Hazard ratio (95% CI)</td>
<td>0.49 (0.38 to 0.64); p&lt;0.00001</td>
<td></td>
</tr>
<tr>
<td>Hazard ratio by TPS score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPS&lt;1%</td>
<td>0.59 (0.38, 0.92); p&lt;0.00951</td>
<td></td>
</tr>
<tr>
<td>TPS 1 to 49%</td>
<td>0.55 (0.34, 0.90); p&lt;0.00808</td>
<td></td>
</tr>
<tr>
<td>TPS&gt;50%</td>
<td>0.42 (0.26, 0.68); p&lt;0.00012</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** ITT, intention to treat; CI, confidence interval; OS, overall survival; TPS, tumour proportion score.

The committee noted the results showed a large difference in overall survival at 12 months. The results were consistent regardless of tumour proportion score expression (see table 1). The committee noted that the median duration of follow-up in the trial (10.5 months) is very short. This made it difficult to know if pembrolizumab combination will continue to have a large benefit on overall survival in the long term. The committee was aware that further data will be available from KEYNOTE-189 and that this should help to reduce the uncertainty in the overall survival estimates. The committee concluded that pembrolizumab improves overall survival compared with standard
care, but the size of the benefit in the long term is unclear.

Indirect treatment comparisons

Pembrolizumab combination improves overall survival compared with chemotherapy plus carboplatin or cisplatin

3.5 The company did a network meta-analysis to compare pembrolizumab combination with other chemotherapy treatments used in NHS clinical practice. These included pemetrexed with carboplatin or cisplatin, or chemotherapy (that is, gemcitabine, paclitaxel, vinorelbine, or docetaxel) with carboplatin or cisplatin. The analysis (which included 17 studies) showed a statistically significant improvement in overall survival with pembrolizumab combination compared with all treatments. The largest benefit was for the comparison with paclitaxel plus carboplatin or cisplatin (hazard ratio [HR] 0.40, 95% credible interval [CrI] 0.25 to 0.63). The ERG noted that although the results suggested that pembrolizumab combination showed a large increase in overall survival, there was heterogeneity between the studies. The committee was satisfied with the methods used by the company and concluded that pembrolizumab combination improves overall survival compared with chemotherapy plus carboplatin or cisplatin.

There is no difference in overall survival between pembrolizumab combination and pembrolizumab monotherapy for people whose tumours express at least a 50% tumour proportion score

3.6 The company did an indirect treatment comparison to compare pembrolizumab combination with pembrolizumab monotherapy for people whose tumours express PD-L1 with at least a 50% tumour proportion score. To inform the clinical effectiveness of pembrolizumab monotherapy, data from KEYNOTE-024 were used. KEYNOTE-024 compared pembrolizumab monotherapy with pemetrexed plus carboplatin or cisplatin. Patients with non-squamous tumours expressing at least a 50% tumour proportion score were selected from both studies. The results showed that pembrolizumab combination therapy is associated with a non-statistically significant increase in overall survival compared with pembrolizumab monotherapy. The committee noted that although the effect was large, the 95% confidence intervals around the effect were very wide. The ERG noted that the company had not included data from
another relevant trial, KEYNOTE-021G (an ongoing open-label phase II study comparing pembrolizumab combination with chemotherapy alone). The company explained that because overall survival was a secondary end point in KEYNOTE-021G, it was not powered to detect changes and therefore excluded it from its analysis. The committee considered that individual patient data from KEYNOTE-021G should have been included in the analysis because they were relevant to the comparison, but agreed that it would not have had a substantial effect on the final effect estimates. The committee was aware that further data will be available from KEYNOTE-189 and this could help to reduce the uncertainty in the overall survival estimates for pembrolizumab combination therapy (see section 3.4). The committee concluded that based on current evidence, there was no difference in overall survival for pembrolizumab combination compared with pembrolizumab monotherapy for people with PD-L1-positive disease whose tumours express PD-L1 with at least a 50% tumour proportion score.

Cost effectiveness

The company's modelling approach was acceptable

The company stated that its model design was a 3-state partitioned survival model which included a 2-year treatment stopping rule and a lifetime treatment effect. The ERG explained that the model structure was not a 3-state partitioned survival model. It noted that to estimate quality-adjusted life years (QALYs), the company's model used 4 states with a time-to-death approach (see section 3.11) and 3 states to estimate costs based on intent of treatment. The committee was aware that this was the same approach taken in NICE's technology appraisal guidance on pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer. Although the committee had concerns about the method used to estimate QALYs, it concluded that company's model was acceptable.

Including a 2-year treatment stopping rule is acceptable

The company included a 2-year treatment stopping rule in the model. The committee was aware that the maximum possible treatment duration with pembrolizumab combination in KEYNOTE-189 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 clinical experts explained that the best treatment duration with pembrolizumab combination is uncertain. The committee noted that implementing a 2-year stopping rule was consistent with NICE’s technology appraisal guidance on pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer. The committee was aware that in that guidance, the recommendation stated treatment should be stopped at 2 years of uninterrupted treatment or earlier if the disease progresses. The committee understood that in clinical practice, people would be able to have treatment breaks to recover from any toxicities associated with pembrolizumab combination and that this would not be considered as interrupted treatment. The committee concluded that the best treatment duration with pembrolizumab combination was unknown and therefore a 2-year treatment stopping rule in line with the clinical and cost-effectiveness evidence is acceptable.

A 5-year survival rate of 5% to 11% for standard care is reasonable for decision making

3.9 In NICE’s technology appraisal guidance on pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer, the committee agreed that the estimated 5-year survival in the standard care arm was between 8% and 11%. The committee was aware that the population considered in that appraisal included people with either squamous or non-squamous disease expressing a tumour proportion score of at least 50%. The clinical experts explained that 5-year overall survival for people with only non-squamous tumours may be lower than 8% to 11% because these patients are not as fit as those with squamous tumours. The clinical lead for the Cancer Drugs Fund noted that the 5-year overall survival from the 2010 Surveillance, Epidemiology, and End Results Program (SEER) database for patients that did not have pembrolizumab monotherapy is about 5%. The committee concluded that a survival rate of between 5% and 11% at 5 years for standard care was reasonable for its decision making.

More mature data on overall survival are needed to inform long-term model predictions

3.10 To extrapolate overall survival for pembrolizumab combination compared with standard care in the intention-to-treat population, a 2-phase piecewise model
with an exponential distribution at a 28 week cut-off was chosen by the company. The ERG did not consider that this approach was appropriate because the exponential distribution provided the worst statistical fit for standard care and produced clinically implausible estimates of overall survival at 5 years for standard care (see section 3.9). Also, because the proportional hazards assumption did not hold (because of changes seen in the hazard ratios over time) the exponential distribution is not appropriate to use. The ERG preferred a fully-fitted parameterised curve using the log-logistic distribution from week 0. Although various curves can be fitted to the Kaplan–Meier data, the log-logistic was statistically the best fitting curve and had clinically plausible 5-year overall survival estimates of 8% for standard care. The committee understood that in previous technology appraisals for this disease area, piecewise models had been used. The committee agreed that there were potentially plausible curves which provided clinically plausible 5-year overall survival for the standard care arm. These included the log-logistic and generalised gamma curves. However, the committee concluded that because of the short median duration of follow-up in the trial (see section 3.4), they could not with any certainty, choose the most appropriate method for extrapolating the overall survival data.

A long-term treatment effect of pembrolizumab combination after stopping treatment is plausible but its duration is uncertain

3.11 The company's base case included a lifetime treatment effect with pembrolizumab combination. The committee considered that the duration of treatment effect is an area of uncertainty for new immunotherapies. The committee was aware that in previous technology appraisals in this disease area, scenarios of a treatment effect lasting between 3 and 5 years had been considered. It was also aware that there is no evidence to inform the long-term treatment effect of pembrolizumab combination from KEYNOTE-189 or any other sources. The committee agreed that, although it was biologically plausible for the treatment effect to continue after stopping pembrolizumab combination, its duration was uncertain. The committee concluded that the ERG's scenarios that included a treatment effect lasting between 3 and 5 years from the start of treatment were appropriate for decision making.

A combined approach to estimating utility values is preferred

3.12 The committee discussed the company's time-to-death approach to estimate
utility values using EQ-5D data from KEYNOTE-189. Utility values for pembrolizumab combination and standard care were pooled and divided into 4 groups based on time to death (from less than 30 days to at least 360 days). The committee was aware that this approach was used in NICE’s technology appraisal guidance on pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer. Clinical experts noted that progression status was equally important to consider when estimating quality of life in people with NSCLC because in clinical practice, notable change in quality of life is seen when disease progresses in people on first-line treatment. The ERG had included 2 scenarios which combined the time-to-death approach and progression based utility values. The first approach used time to death, with a quality-of-life decrement associated with progressive disease applied for patients who had progressed and the second used progression status with a quality-of-life decrement associated with time to death of less than 360 days applied for patients who are likely to live less than 360 days. The committee noted that although there are some issues with the time-to-death approach (that is, data from a large number of patients are not available to analyse because they do not qualify for any of the health states used in the approach), they preferred a combined approach to estimating utility values to fully capture the quality-of-life changes for people with NSCLC.

The most plausible ICERs for pembrolizumab combination compared with pemetrexed plus carboplatin or cisplatin are highly uncertain

3.13 The committee considered the incremental cost-effectiveness ratios (ICERs) presented by the company which included the commercial arrangement for pembrolizumab. The ERG also incorporated the commercial arrangement for pemetrexed maintenance therapy. The exact ICERs cannot be reported because the commercial arrangements are confidential. The results showed that in the company’s base case, the ICER was less than £50,000 per QALY gained. The committee considered the ERG’s preferred base case which included the following changes:

- correcting coding errors
- adjustment for background mortality (because of the relatively short length of follow-up for the trial compared with the model time horizon)
• removing the cost of PD-L1 testing in both arms because it is now routine in NHS practice (see section 3.2)

• fully parameterised curves from week 0 using the log-logistic extrapolation (see section 3.9).

The results of the ERG’s preferred base case, which included the confidential commercial arrangements for pembrolizumab and pemetrexed maintenance therapy gave an ICER below £50,000 per QALY gained. The committee accepted the ERG’s adjustment for background mortality, corrections of coding errors and removal of PD-L1 testing but recalled its other preferred modelling assumptions which were:

• a 2 year stopping rule (see section 3.7)

• 3- to 5-year duration of treatment effect after starting treatment (see section 3.10)

• a combined approach to estimating utility values (see section 3.10)

• a 5-year overall survival estimate in the standard care arm of 5% to 11% (see section 3.8).

Using the ERG’s scenarios, the range of ICER’s produced using the commercial arrangements were below £50,000 per QALY gained (using a log-normal curve to extrapolate overall survival from week 0 with a 5-year duration of treatment effect) and above £50,000 per QALY gained (using a generalised gamma curve to extrapolate overall survival with a 5-year duration of treatment effect). The committee also noted that with a 3 year duration of treatment effect and a combined approach to estimating utility values, the ICER will likely increase. The committee was concerned that because the trial data are immature and overall survival has not been reached in the pembrolizumab combination arm (see section 3.4) it could not, with any certainty, conclude that the most plausible ICER is below £50,000 per QALY gained without further evidence.

**The most plausible ICERs for pembrolizumab combination compared with chemotherapy plus carboplatin or cisplatin are highly uncertain**

3.14 The committee discussed the ICERs for pembrolizumab combination compared with chemotherapy (paclitaxel, docetaxel, gemcitabine, and vinorelbine) plus carboplatin or cisplatin. It noted that in the company’s base case, with the
confidential commercial arrangements for pembrolizumab and pemetrexed maintenance therapy, the ICERs were all above £50,000 per QALY gained. Using the ERG’s preferred assumptions (see section 3.12) the ICERs ranged from below £50,000 per QALY gained for the comparison with gemcitabine plus carboplatin or cisplatin and above £50,000 per QALY gained for the comparison with vinorelbine plus carboplatin or cisplatin. The committee noted that these would all likely increase once the committee’s preferred assumptions were applied (see section 3.12). The committee was aware that the results are not generated from a direct comparison and more data on overall survival from KEYNOTE-189 (see section 3.4) would help to address the uncertainty. The committee could not, with any certainty, conclude that the most plausible ICER is below £50,000 per QALY gained without further evidence.

The most plausible ICERs for pembrolizumab combination compared with pembrolizumab monotherapy for people whose tumours express at least a 50% tumour proportion score are uncertain

3.15 The committee discussed the ICERs for pembrolizumab combination compared with pembrolizumab monotherapy for those people whose tumours express a tumour proportion score of at least 50%. It noted that in both the company’s and ERG’s base case, using the confidential commercial arrangements for pembrolizumab and pemetrexed maintenance therapy the ICER was below £30,000 per QALY gained. The committee was aware that the indirect treatment comparison which informed this analysis had wide credible confidence intervals and showed no difference in overall survival between the 2 treatments (see section 3.6). The committee was aware that the results are not generated from a direct comparison and more data on overall survival from KEYNOTE-189 (see section 3.4) would help to address some of this uncertainty. The committee could not, with any certainty, conclude that the most plausible ICER is below £30,000 per QALY gained without further evidence.

Innovation

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

3.16 The committee considered the innovative nature of pembrolizumab
combination. The patient and clinical experts explained that in the past 20 years, there have been few improvements for untreated, metastatic, non-squamous NSCLC in people whose tumours have no EGFR- or ALK-positive mutations. There is an important unmet need for people with this condition. The clinical experts also said that pembrolizumab combination is innovative in its potential to have a substantial effect on health-related benefits. The committee understood that improvements in survival and reduced adverse effects are important for people with this condition. It concluded that pembrolizumab combination could be considered an important treatment option for this population, but there were no additional benefits associated with this treatment that had not been captured in the economic analysis.

End of life

Pembrolizumab combination compared with chemotherapy (both plus carboplatin or cisplatin) meet NICE’s end-of-life criteria

3.17 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE’s Cancer Drugs Fund technology appraisal process and methods. The committee discussed whether life expectancy for this population would be less than 24 months. The committee was aware that for this population, the relevant comparators were pemetrexed with carboplatin or cisplatin (standard care in KEYNOTE-189) or chemotherapy with carboplatin or cisplatin. It noted that these treatments are usually used for people whose tumours express a tumour proportion score of less than 50%. In the company’s base case, the modelled mean overall survival in the standard care arm was 15 months for people whose tumours express a tumour proportion score of less than 50%. The committee concluded that the short life expectancy criterion was met. The modelled mean number of months of life gained with pembrolizumab combination compared with standard care in the company’s base case was 8 months. The committee further noted that for people whose tumours express a tumour proportion score of between 1% and 49%, the modelled difference in mean overall survival with pembrolizumab combination was 19 months compared with standard care. For the comparison with chemotherapy plus carboplatin or cisplatin the committee recalled that in the company’s network meta-analysis (see section 3.5), there was large treatment benefit with pembrolizumab combination. The committee considered it reasonable to assume that the survival benefit with pembrolizumab
combination is likely to exceed 3 months and concluded that it met the end-of-life criteria for this population.

**Pembrolizumab combination compared with pembrolizumab monotherapy for people whose tumours express at least a 50% tumour proportion score does not meet NICE's end-of-life criteria**

3.18 The committee discussed whether life expectancy for this population would be less than 24 months. The committee noted that the short life expectancy criterion may not be met because the company's modelled mean overall survival with pembrolizumab monotherapy is 28 months. However, because of the uncertainty of the indirect treatment comparison results which informed this analysis (see section 3.6), it is not clear if life expectancy is less than 24 months for this population. Also, the committee noted that although the company's modelled mean extension to life was more than 3 months, the results of the company's indirect treatment comparison showed no statistically significant difference in overall survival between pembrolizumab combination and pembrolizumab monotherapy in people whose tumours express a tumour proportion score of at least 50% (see section 3.6). The committee concluded that pembrolizumab combination compared with pembrolizumab monotherapy in people whose tumours express a tumour proportion score of at least 50% did not meet the end-of-life criteria.

**Conclusion**

**Pembrolizumab combination is not recommended for routine use**

3.19 The long-term overall survival benefit with pembrolizumab combination was uncertain because median overall survival in the pembrolizumab combination arm of KEYNOTE-189 had not been reached at the most recent data cut (see section 3.4). This resulted in uncertain estimates for overall survival for pembrolizumab combination compared with chemotherapy plus carboplatin or cisplatin and pembrolizumab monotherapy. After taking into account its preferred modelling assumptions and NICE’s criteria on end of life, the committee considered that the ICERs were not all clearly within the range usually considered a cost-effective use of resources. The committee concluded not to recommend pembrolizumab combination for routine use in adults with untreated, metastatic, non-squamous NSCLC whose tumours have no EGFR- or
ALK- positive mutations.

Cancer Drugs Fund

Pembrolizumab combination is recommended for use within the Cancer Drugs Fund

3.20 Having concluded that pembrolizumab combination could not be recommended for routine use, the committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting the addendum to the NICE process and methods guides. The committee noted that there was uncertainty about the long-term survival with pembrolizumab combination. The committee was aware that further data on overall survival would be available from KEYNOTE-189 because patients are still being followed up. The committee understood that the data from KEYNOTE-189 would provide evidence to address uncertainties in the clinical-effectiveness evidence including whether pembrolizumab combination improves overall survival compared with:

- pemetrexed plus carboplatin or cisplatin in the intention-to-treat population and for those people whose tumours express a tumour proportion score of less than 50%
- chemotherapy plus carboplatin or cisplatin in the intention-to-treat population and for those people whose tumours express a tumour proportion score of less than 50%
- pembrolizumab monotherapy in people whose tumours express a tumour proportion score of 50% or more.

The committee discussed whether there was potential for pembrolizumab to be cost effective. It recalled its conclusion that the current cost-effectiveness results were very uncertain but some scenarios were within the range considered a cost-effective use of NHS resources. It agreed that with longer follow-up data on overall survival, pembrolizumab combination has the potential to be cost effective. The committee concluded that pembrolizumab combination met the criteria to be considered for inclusion in the Cancer Drugs Fund. It recommended pembrolizumab combination for use within the Cancer Drugs Fund as an option for untreated, metastatic, non-squamous NSCLC, in adults whose tumours have no EGFR- or ALK-positive mutations, if treatment does not exceed 2 years and 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, non-squamous non-small-cell lung cancer whose tumours have no epidermal growth factor receptor- or anaplastic lymphoma kinase-positive tumour mutations and the doctor responsible for their care thinks that pembrolizumab combination 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 latter.
5 Recommendations for data collection

5.1 Proposals for further data collection in the Cancer Drugs Fund include:

- Overall survival from KEYNOTE-189
6 Appraisal committee members and NICE project team

Appraisal committee members

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

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

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

NICE project team

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

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