

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final appraisal determination

**Pembrolizumab for untreated PD-L1-positive
metastatic non-small-cell lung cancer**

1 Recommendations

1.1 Pembrolizumab is recommended for use within the Cancer Drugs Fund as an option for untreated PD-L1-positive metastatic non-small-cell lung cancer in adults, only if:

- their tumours express PD-L1 with at least a 50% tumour proportion score and have no epidermal growth factor receptor- or anaplastic lymphoma kinase-positive mutations
- pembrolizumab is stopped at 2 years of uninterrupted treatment and no documented disease progression
- the conditions in the managed access agreement for pembrolizumab are followed.

1.2 This recommendation is not intended to affect treatment with pembrolizumab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

2 The technology

Description of the technology	Pembrolizumab (Keytruda, Merck, Sharp & Dohme) is a humanised monoclonal antibody that acts on the 'programmed death 1' protein (PD-1). The PD-1 protein is part of the immune checkpoint pathway, and blocking its activity may promote an anti-tumour immune response.
Marketing authorisation	Pembrolizumab has a marketing authorisation for the first-line treatment of metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with at least a 50% tumour proportion score with no epidermal growth factor receptor or anaplastic lymphoma kinase-positive tumour mutations.
Adverse reactions	The most common treatment-related adverse events associated with pembrolizumab include fatigue, decreased appetite, nausea, rash and pruritus. For full details of adverse reactions and contraindications, see the summary of product characteristics.
Recommended dose and schedule	200 mg every 3 weeks by intravenous (IV) infusion The summary of product characteristics recommends treatment with pembrolizumab until disease progression or unacceptable toxicity.
Price	<p>Pembrolizumab is available at a cost of £1,315.00 per 50 mg vial (excluding VAT; British national formulary online, accessed March 2017).</p> <p>The pricing arrangement considered during guidance development was that the company had agreed a patient access scheme with the Department of Health. This scheme would provide a simple discount to the list price of pembrolizumab with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.</p> <p>The managed access agreement agreed between the company and NHS England will replace this patient access scheme.</p>

3 Evidence

The appraisal committee ([section 8](#)) considered evidence submitted by Merck Sharp & Dohme and a review of this submission by the evidence review group. See the [committee papers](#) for full details of the evidence.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of pembrolizumab, having considered evidence on the nature of untreated PD-L1-positive metastatic non-small-cell lung cancer (NSCLC) and the value placed on the benefits of pembrolizumab by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical management

- 4.1 The committee heard from the clinical experts that people with untreated metastatic NSCLC whose tumours express PD-L1 with at least a 50% tumour proportion score and who have no epidermal growth factor receptor (EGFR)- or anaplastic lymphoma kinase (ALK)-positive tumour mutations have limited treatment options. It understood that patients can be on treatment for a long time and this can cause unpleasant side effects. Symptoms such as breathlessness and cough are difficult to treat. The clinical experts explained that new treatments which offer survival benefits with fewer side effects compared with standard care are needed in this population. The patient experts explained that symptoms can be debilitating, and that improving quality of life and even small extensions in length of life are of considerable importance to this patient group. The committee heard from the clinical experts that pembrolizumab was innovative in its potential to make a significant and substantial effect on health-related benefits. It understood that pembrolizumab is generally well tolerated. The committee concluded that pembrolizumab is an important treatment option for people with untreated metastatic PD-L1-positive NSCLC.

- 4.2 The committee noted that the marketing authorisation for pembrolizumab only includes people with untreated metastatic NSCLC if their tumour expresses PD-L1 with at least a 50% tumour proportion score. It heard from NHS England that all lung cancers will be tested for PD-L1 status from April 2017. The committee heard from the clinical expert that testing involves an immunohistochemical assay and facilities are widely available in histopathology laboratories already. However, the clinical expert noted that PD-L1 tests are complex to interpret and the standard time needed for assessment is 20 minutes. The committee was aware that although the company had included the cost of the assay in the economic model, the time needed to assess the sample had not been accounted for. The committee concluded that PD-L1 testing could be standardised quickly and, with training, implemented as standard clinical practice in the NHS.
- 4.3 The committee understood that management of untreated metastatic PD-L1-positive NSCLC in clinical practice is platinum-based combination chemotherapy (that is, docetaxel, gemcitabine, paclitaxel or vinorelbine plus a platinum-based drug), and that docetaxel, gemcitabine, paclitaxel or vinorelbine alone (single-agent therapy) is recommended for patients who cannot tolerate combination therapy (NICE's guideline on [lung cancer diagnosis and management](#)). NICE's technology appraisal guidance on [pemetrexed for the first-line treatment of NSCLC](#) recommends pemetrexed with cisplatin for adenocarcinoma or large-cell carcinoma. Pemetrexed is also recommended as a maintenance treatment for locally advanced or metastatic non-squamous NSCLC in adults whose disease has not progressed after pemetrexed and cisplatin therapy (NICE technology appraisal guidance on [pemetrexed maintenance treatment for non-squamous NSCLC after pemetrexed and cisplatin](#)), and after platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel (NICE technology appraisal guidance on [pemetrexed for the maintenance treatment of NSCLC](#)). The committee understood that pembrolizumab would be considered as an alternative to platinum-based

combination therapy, single-agent chemotherapy, or pemetrexed and cisplatin therapy. The committee concluded that pembrolizumab was appropriately positioned in the clinical pathway as an option for people with untreated metastatic PD-L1-positive NSCLC, that is, as an alternative to platinum-based combination therapy, single-agent chemotherapy, or pemetrexed and cisplatin therapy.

Clinical effectiveness

- 4.4 The committee noted that the clinical-effectiveness evidence for pembrolizumab came from KEYNOTE-024. This was an open-label, phase III, randomised controlled trial comparing pembrolizumab with standard care. Standard care therapies included platinum-based combinations with either gemcitabine or paclitaxel, and a platinum-based combination with pemetrexed (with or without pemetrexed maintenance for non-squamous disease). The committee heard from the evidence review group (ERG) that no evidence was available for single-agent chemotherapy, and the clinical experts noted that single-agent chemotherapy is predominantly used as an option for previously treated disease. The committee heard from the clinical experts that although fewer patients had a pemetrexed-containing regimen in KEYNOTE-024 than expected, they considered that the standard care treatments were likely to be the same as those used in clinical practice in England. The committee was aware that the inclusion criteria in KEYNOTE-024 were that patients had untreated stage IV metastatic PD-L1-positive NSCLC (whose tumours express at least 50% PD-L1 and no EGFR- or ALK-positive mutations) with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The committee heard from the clinical experts that although the proportion of patients with squamous disease was smaller than expected, and stage III patients were not included in KEYNOTE-024, the overall population in KEYNOTE-024 was comparable to clinical practice in England. The committee therefore concluded that KEYNOTE-024 was generalisable to clinical practice in England.

4.5 The committee was aware that the median overall survival was not reached in KEYNOTE-024. There were 44 and 64 deaths in the pembrolizumab and standard care arms respectively. The committee noted that both the intention-to-treat results (hazard ratio [HR] 0.60; 95% confidence interval (CI) 0.41 to 0.89) and the crossover adjusted results (HR 0.50; 95% CI 0.34 to 0.76) suggested a statistically significant survival benefit for pembrolizumab compared with standard care. This was confirmed by the updated 19-month median follow-up intention-to-treat overall survival results which the company presented during consultation (the results were submitted as academic in confidence). The committee concluded that based on the trial data, pembrolizumab had an important extension-to-life benefit for people with untreated metastatic PD-L1-positive NSCLC compared with standard care.

Overall survival data

4.6 The committee was aware that the trial's data and safety monitoring committee recommended that KEYNOTE-024 should be stopped at the second interim analysis to give patients in the standard care arm the opportunity to have pembrolizumab. At this time, only 35% of the total number of expected overall survival events had occurred and median overall survival had not been reached in either of the trial arms. The ERG highlighted that the immaturity of the overall survival data and the high level of crossover (43.7% of standard care arm patients had pembrolizumab at second interim analysis) limits the reliability of the survival data collected in KEYNOTE-024. The ERG agreed with the company that the 2-stage method was the most appropriate method for the crossover adjustment. It also noted that regardless of the crossover adjustment method used, the survival data remained uncertain as the assumption of proportional hazards was invalid. The committee agreed that the 2-stage crossover adjustment method was the most appropriate, but that any estimate of overall survival was subject to uncertainty. The committee concluded that although there was sufficient evidence that

pembrolizumab has an important extension-to-life benefit in people with untreated stage IV metastatic PD-L1-positive NSCLC compared with standard care, the exact size of the overall survival gain was uncertain because of the immaturity of the data.

Treatment duration

4.7 The committee was aware that the maximum possible treatment duration with pembrolizumab in KEYNOTE-024 was 2 years (35 cycles). The committee noted that, despite 2 years maximum treatment duration in the trial protocol, the summary of product characteristics states that treatment should continue until disease progression or unacceptable toxicity. The committee heard from the ERG that no patients in the pembrolizumab arm had completed 2 years' therapy. The committee heard from clinical experts that the best duration of treatment with pembrolizumab is unknown. The clinical and patient experts stated that although pembrolizumab has low toxicity, long durations of intravenous infusions can be a burden to patients. They further agreed that stopping treatment at 2 years independent of disease status would be acceptable to patients. The committee noted comments from NHS England that benefits to patients may occur when the immune system responds sufficiently to the treatment against the cancer, and patients may not need continued treatment until disease progression. The committee concluded that limiting pembrolizumab treatment to 2 years is clinically plausible, but the best treatment duration is unknown.

Cost effectiveness

4.8 The committee discussed the company's cost-effectiveness evidence and the ERG's review. It accepted the structure of the company's economic model and considered it appropriate for decision-making.

Stopping rule

4.9 The committee discussed the assumption in the company's model that at 2 years, all patients, including patients whose disease had not progressed, would stop treatment. It understood that this assumption was based on the KEYNOTE-024 protocol. The ERG exploratory analyses varied the maximum time on treatment. These analyses increased the company original base-case incremental cost-effectiveness ratio (ICER) from £41,213 per quality-adjusted life year (QALY) gained to £51,925 per QALY gained for 3 years on treatment, and up to £84,868 per QALY gained for lifetime treatment. The committee heard from NHS England that it will track biopsy samples with a tumour proportion score of at least 50% and would only commission pembrolizumab for untreated disease (performance status 0 to 1) for a maximum treatment duration of 2 years based on the trial evidence. NHS England further stated that, if NHS trusts continue treatment beyond 2 years for individual patients, NHS England will not reimburse them for this non-commissioned use of the drug. The committee recalled its conclusion that limiting pembrolizumab treatment to 2 years is clinically plausible, and that patient and clinical experts agreed that stopping treatment at 2 years independent of disease status would be acceptable to patients (see section 4.7). The committee concluded that implementing a 2-year stopping rule in the model was appropriate.

Overall survival extrapolation

4.10 The committee noted that in the company's sensitivity analyses, the first and the third most influential parameter in the cost-effectiveness analysis was the extrapolation of overall survival in the pembrolizumab and standard care arms. To estimate overall survival, the company used 22-week Kaplan–Meier data from KEYNOTE-024. After 22 weeks, the company fitted separate exponential models to the data (with the 2-stage crossover adjustment for the standard care arm). In its original scenario analyses, the company explored an alternative timepoint of 4 weeks at which to extrapolate the data and a fully fitted parametric approach to the

trial data. Both these analyses increased the company's original base-case ICER by more than 20%. The ERG highlighted that 57% of the QALYs attributable to treatment with pembrolizumab were generated during a period in which there was no direct evidence of effect from any clinical trials, and so there was high uncertainty about the overall survival projection. The committee heard from the ERG that the company extrapolations of overall survival Kaplan–Meier data from KEYNOTE-024, together with Akaike information criterion and Bayesian information criterion tests done by the company, show that all of the standard distributions that could be selected to extrapolate the trial data are each as statistically likely (or unlikely) as each other. Confidence in any distribution decreases as time from the last available trial data point increases. The ERG noted that by using an exponential distribution for overall survival extrapolation, the company had assumed a constant mortality rate for both pembrolizumab and standard care arms after week 22. This mortality rate was higher for standard care than for pembrolizumab across the 20-year time horizon of the model, effectively meaning that pembrolizumab continued to have a treatment effect many years after treatment could have stopped. The ERG stated that the uncertainty around the overall survival extrapolation even at 2 years is the main source of uncertainty in the cost-effectiveness analyses. The committee concluded that there was a high level of uncertainty around the extrapolation of overall survival data and the long-term treatment effect.

- 4.11 The committee was disappointed that the company had only modelled a constant mortality rate for pembrolizumab after week 22, because this was unlikely based on current clinical understanding of disease progression. It noted that the duration of continued treatment effect is an area of uncertainty for new immunotherapies, and it would have preferred to see scenarios in which the hazard ratio for overall survival was set to 1 at different timepoints to model stopping of the continued treatment effect. The committee was not shown any evidence to determine the impact of

this uncertainty. It agreed that based on the data available, the most appropriate method of overall survival extrapolation is hard to determine. The ERG noted that, because of the immaturity of the overall survival data, there is no distribution that can be considered reliable and highlighted that the company scenario analyses were sensitive to extrapolating overall survival at different timepoints (section 4.10). The committee concluded that the company's choice of the 22-week cut-off point at which to extrapolate the Kaplan–Meier data from KEYNOTE-024 was plausible, however because of the high level of uncertainty around the extrapolation of overall survival data, other timepoints are equally plausible.

- 4.12 During consultation the company provided 19 months' follow-up overall survival data from KEYNOTE-024 to update the cost-effectiveness analyses. The ERG considered that the additional Kaplan–Meier data reduced uncertainty in the overall survival projection for the pembrolizumab arm. The company's updated base-case ICER (using 22-week updated Kaplan–Meier data to extrapolate survival) was £42,295 per QALY gained. The company explored alternative timepoints of 14 and 30 weeks at which to extrapolate the trial data; this increased the updated ICER to £45,813 and £44,150 per QALY gained respectively. The committee recalled its previous conclusion that the most appropriate method of overall survival extrapolation is hard to determine (see sections 4.10 to 4.12), and noted that all 3 cost-effectiveness analyses with the updated overall survival data were higher than the original base-case ICER of £41,213 per QALY gained. The committee concluded that all time points given for extrapolation (22-, 14- and 30-weeks) are equally plausible. It therefore considered a range of ICERs to account to for this.
- 4.13 In the company's original base-case, the overall survival projection for patients having standard care was 1.9% at 5 years. The ERG noted that National Lung Cancer Audit (NLCA) 2006 to 2010 data suggest that 5-

year survival with stage IV ECOG performance status 0 to 1 NSCLC is 5.0%. In the analyses using the updated overall survival data, the 5-year extrapolated survival in the standard care arm was 2.4, 2.7, and 4.5% for the 22-week, 14-week, and 30-week cut-off points respectively (see section 4.12 for the corresponding ICERs). The committee noted that the 5-year survival estimate at the latest cut-point was close to the NCLA estimate. The ERG highlighted that the NLCA dataset is a reliable source of evidence but not all patients had chemotherapy (which has been shown to extend life), so 5.0% is likely to be an underestimate of the survival rate. The clinical experts argued that most of the NLCA patients would have had some form of therapy and that patients with EGFR mutation-positive tumours have a better survival prognosis; if the data included any patients with EGFR mutation-positive tumours, the survival estimates may be higher compared with patients without the mutation. The company commented that the NLCA estimate is not reliable because it is based on incomplete data. Instead, the company presented a Cancer Analysis System estimate (using complete 2001 to 2011 data) for stage IV NSCLC of 1.6% at 5 years (not specified by ECOG performance status and including EGFR- or ALK- positive tumour mutations). The ERG noted that this estimate was not performance status-specific and therefore not comparable to overall survival in KEYNOTE-024. It stated that the NLCA's estimate of 5.0% at 5 years remains the most plausible estimate of overall survival for patients with untreated stage IV, performance status of 0 to 1, metastatic PD-L1-positive NSCLC who are having chemotherapy in a trial setting. The clinical experts agreed that while it may be an upper estimate, the NLCA estimate of 5.0% is reasonable for this patient group. The committee acknowledged that the 5-year overall survival rate for patients in the standard care arm could be between 2.4% and 5.0%. Given the immaturity of the trial data, and the uncertainty around the extrapolation of overall survival (see sections 4.10 to 4.12), the committee considered that the most reliable overall survival estimate for the standard of care arm at

this point, was that from the published NLCA. It concluded that the analyses which used a survival rate of 5% at 5 years for the standard care arm were the most appropriate on which to base its decision.

Utility values

4.14 The committee discussed the utility data used in the company model. It noted that EQ-5D data were collected in KEYNOTE-024; these data are the preferred measure of health-related quality of life in adults. The utility values for pembrolizumab and standard care were pooled (adjusted for age) and divided into 4 groups based on time to death (from less than 30 days to at least 360 days). The committee noted that in the company's sensitivity analyses, the utility values for long-term survivors were the second most influential parameter in the cost-effectiveness analysis. The committee understood that given the number of patients in KEYNOTE-024 (n=305), dividing the utility data into 4 groups based on time to death may have increased the uncertainty around the utility values for each state. The ERG highlighted that the utilities derived from KEYNOTE-024 were also implausibly high; the values at 360 days before death were higher than the UK population norm for people of the same age. The committee was aware that in KEYNOTE-024, 87% of patients in the standard care arm and 97% of patients in the pembrolizumab arm were current or former smokers which is higher than in the general population. It also recognised that the utility values from KEYNOTE-024 used the tariff derived from a representative sample of the UK population and values from patients with the condition. The ERG noted that while the utility of individuals with metastatic lung cancer could be higher than the population norm, NICE Reference Case methods specified the use of a general population utility tariff applied to patient quality-of-life data. The committee also considered that the utility values did not support the evidence in the company's submission, which described patients with NSCLC as having the highest prevalence of psychological distress (3 times more than in other cancers), leading to a poorer prognosis and greater patient burden. The committee

agreed with the ERG that the utility values from KEYNOTE-024 appeared implausible and did not seem in line with the physical symptoms described by the patient experts.

- 4.15 The committee considered the analyses presented where the utility values for at least 360 days to death were set to the UK population norm. Using the UK population norm capped utilities increased the original base-case ICER to £42,152 per QALY gained. The ERG explored using alternative utility values from NICE's technology appraisal guidance on [pemetrexed for treating non-small-cell lung cancer](#) which increased this ICER by approximately £7,000 to £49,247 per QALY gained. The company's updated analyses with 5-year survival in the standard care arm of 5% and using the UK population norm capped utilities resulted in ICERs of £49,897, £54,577 and £46,083 per QALY gained for 22-week, 14-week, and 30-week extrapolation timepoints respectively. However, the committee agreed that simply adjusting utility to the population norm is still a conservative assumption given the clear physical symptoms and psychological distress reported by patients with NSCLC. Analyses using utilities from NICE's guidance on pemetrexed would further increase the ICERs by approximately £7,000 per QALY gained. The ERG noted that the scenario that used utility values from NICE's guidance on pemetrexed did not use time to death utilities, and therefore represents only an exploratory analysis. Accounting for the uncertainty in the utility values, the committee concluded that that the ICER would likely fall between that from the analysis setting the utility for 360 days to death to that of the UK population norm and the analysis using utilities from the pemetrexed guidance.

ICERs for decision-making

- 4.16 The committee discussed the ICERs for pembrolizumab compared with standard care. It was aware that the company's revised base-case ICER of £42,295 per QALY did not address the committee's conclusions on the

key assumptions (utility values and overall survival in the standard care arm at 5 years). The committee agreed that, although the choice of overall survival extrapolation could have a very large effect on the cost-effectiveness estimates, the data were so immature that any estimate of overall survival was extremely uncertain. The committee noted the ICER range of £46,083 per QALY gained (survival data extrapolated from 30 weeks) to £54,577 per QALY gained (survival data extrapolated from 14 weeks; see section 4.12), based on 2-year stopping rule (see section 4.9), a 5% overall survival at 5 years for standard care (see section 4.13) and utility value for at least 360 days to death set at the UK population norm value (see section 4.15). However, this ICER range was considered conservative given the utilities were capped to the population norm (see section 4.15). It noted the alternative ERG analyses which used utility values from NICE's pemetrexed guidance, which would increase the ICER by approximately £7,000 per QALY gained. Therefore the ICER range identified by the committee for its decision-making was £46,083 to £61,577 per QALY gained. The committee was aware that there is a commercial access agreement for pemetrexed monotherapy maintenance if used after pemetrexed and cisplatin induction therapy (one of the treatments used in the standard care arm). Including the commercial access agreement in the company's model would further increase these ICERs. The committee also considered that the largest uncertainty was related to the overall survival estimates with an incremental benefit for pembrolizumab that is sustained over the lifetime of the model. No evidence was presented to determine the impact of this uncertainty in terms of a reduced treatment benefit over time. The committee concluded that the ICER range on which it was basing its decision was associated with uncertainty which needed to be accounted for when making its judgement about the acceptability of pembrolizumab as an effective use of NHS resources.

Innovation

4.17 The committee considered the innovative nature of pembrolizumab. It heard from the patient and clinical experts that in the past 20 years there have been few improvements for untreated metastatic NSCLC in people whose tumours have no EGFR- or ALK-positive mutations, and that there is an important unmet need for people with this condition. It understood that improvements in survival and reduced adverse effects are important for people with this condition. The committee concluded that pembrolizumab 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 considerations

4.18 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 without pembrolizumab would be less than 24 months. It noted evidence from the company which showed that people with NSCLC have an average life expectancy of less than 24 months (9.9 months for patients with squamous disease, and 13.9 months for patients with non-squamous disease). The committee discussed whether a survival benefit of over 3 months can be expected for pembrolizumab compared with standard care. The committee heard that the average number of months of life gained with pembrolizumab, as estimated by the company's economic model, is 29.0 months compared with 14.6 months for standard care. Therefore pembrolizumab may offer, on average, at least 3 months' extension to life compared with standard care. However, the committee noted that there is considerable uncertainty around the validity of the overall survival projection in the company model (see sections 4.6, 4.10 to 4.12). It considered that because of the immaturity of the data for pembrolizumab, any estimate of an overall

survival gain compared with standard care was very uncertain. Based on the evidence given, the committee considered it reasonable to conclude that there was likely to be an overall survival gain for pembrolizumab in the previously untreated population of over 3 months. The committee concluded that pembrolizumab met the life expectancy and life extension criteria to be considered a life-extending, end-of-life treatment.

- 4.19 Given the ICER range and the uncertainties identified (see section 4.16), and considering the risk to the NHS of paying for a treatment that was not cost effective, the committee concluded it could not recommend pembrolizumab for routine use in the NHS for untreated metastatic NSCLC in people with at least a 50% tumour proportion score and no EGFR- or ALK- positive tumour mutations.

Cancer Drugs Fund considerations

- 4.20 Having concluded that pembrolizumab could not be recommended for routine use, the committee then considered if pembrolizumab could be recommended for people with untreated metastatic PD-L1-positive NSCLC within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England, noting NICE's [final Cancer Drugs Fund technology appraisal process and methods](#). The committee was aware of an ongoing randomised, open-label, phase III study of overall survival comparing pembrolizumab with platinum-based chemotherapy in patients with untreated, PD-L1-positive advanced or metastatic NSCLC (KEYNOTE-042). The committee acknowledged that more data will become available for pembrolizumab over time; the estimated completion date for KEYNOTE-042 is February 2018, and the next data analysis for KEYNOTE-024 is in December 2017. The committee acknowledged that the ICER for pembrolizumab compared with standard care was uncertain (see section 4.16), but concluded that pembrolizumab had the plausible potential to satisfy the criteria for routine use, taking into account its

conclusion on the end-of-life criteria (see section 4.19). The committee was aware that although there were uncertainties in the clinical-effectiveness evidence regarding overall survival data from KEYNOTE-024 (see section 4.6), there will be further updates from the trial. In addition, KEYNOTE-042, and updated NLCA and Public Health England data will become available. The committee recognised that these additional long-term survival data would reduce the clinical uncertainty and allow for a more certain cost-effectiveness estimate. It also acknowledged that data collected from use in the NHS through the Cancer Drugs Fund would offer further supportive evidence on the clinical effectiveness of pembrolizumab. The committee was aware that NICE, NHS England and the company will discuss the data collection as part of the managed access agreement. The committee concluded that pembrolizumab met the criteria to be considered for inclusion in the Cancer Drugs Fund, and recommended pembrolizumab as an option for use within the Cancer Drugs Fund for people with untreated stage IV metastatic PD-L1-positive NSCLC (as specified in section 1.1) if the conditions in the managed access agreement for pembrolizumab are followed.

Summary of appraisal committee’s key conclusions

TAXXX	Appraisal title: Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer	Section
Key conclusion		
Pembrolizumab is recommended for use within the Cancer Drugs Fund as an option for untreated PD-L1-positive metastatic non-small-cell lung cancer (NSCLC) in adults only if:	1.1, 4.6, 4.16	

- their tumours express PD-L1 with at least a 50% tumour proportion score and have no epidermal growth factor receptor (EGFR)- or anaplastic lymphoma kinase (ALK)-positive mutations
- pembrolizumab is stopped at 2 years of uninterrupted treatment and no documented disease progression
- the conditions in the managed access agreement for pembrolizumab are followed.

The committee concluded that although there was sufficient evidence that pembrolizumab had an important extension-to-life benefit in people with untreated stage IV metastatic PD-L1-positive NSCLC compared with standard care, the exact size of the overall survival gain was uncertain because of the immaturity of the data.

The ICER range identified by the committee for its decision-making was £46,083 to £61,577 per QALY gained. The committee was aware that there is a commercial access agreement for pemetrexed monotherapy maintenance if used after pemetrexed and cisplatin induction therapy (one of the treatments used in the standard care arm). Including the commercial access agreement in the company's model would further increase these ICERs. The committee considered that the ICER range on which it was basing its decision was associated with uncertainty which needed to be accounted for when making its judgement about the acceptability of pembrolizumab as an effective use of NHS resources.

Current practice

<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>People with untreated metastatic NSCLC whose tumours express at least 50% PD-L1 and who have no EGFR- or ALK-positive tumour mutations have limited treatment options.</p> <p>Platinum-based combination therapy, single-agent chemotherapy, and pemetrexed and cisplatin therapy (with or without pemetrexed maintenance therapy for non-squamous disease) are currently available treatments.</p>	<p>4.1, 4.3</p>
<p>The technology</p>		
<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>People with NSCLC can have debilitating symptoms and improving quality of life is important.</p> <p>Pembrolizumab is generally well tolerated and has an important extension-to-life benefit compared with standard care.</p>	<p>4.1, 4.5</p>

<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>The committee noted that the marketing authorisation for pembrolizumab states that people should have treatment based on their tumour's expression of PD-L1, confirmed by a validated test. It heard from NHS England that all lung cancers will be tested for PD-L1 from April 2017.</p> <p>The committee concluded that pembrolizumab was appropriately positioned in the clinical pathway as an option for people with untreated metastatic PD-L1-positive NSCLC.</p>	<p>4.2, 4.3</p>
<p>Adverse reactions</p>	<p>Pembrolizumab is generally well tolerated.</p>	<p>4.1</p>
<p>Evidence for clinical effectiveness</p>		
<p>Availability, nature and quality of evidence</p>	<p>The clinical-effectiveness evidence for pembrolizumab came from KEYNOTE-024, an open-label, phase III, randomised controlled trial comparing pembrolizumab with standard care (platinum-based combinations with either gemcitabine or paclitaxel, and a platinum-based combination with pemetrexed).</p>	<p>4.4</p>
<p>Relevance to general clinical practice in the NHS</p>	<p>The committee concluded that KEYNOTE-024 is generalisable to clinical practice in England.</p>	<p>4.4</p>

<p>Uncertainties generated by the evidence</p>	<p>Although there was sufficient evidence that pembrolizumab had an important extension-to-life benefit, the exact size of the overall survival gain was uncertain because of the immaturity of the data.</p> <p>The committee concluded that limiting pembrolizumab treatment to 2 years is clinically plausible but that the best treatment duration is unknown.</p>	<p>4.6, 4.7</p>
<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>No clinically relevant subgroups were identified.</p>	<p>–</p>
<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>The exact size of the overall survival gain was uncertain because of the immaturity of the data.</p>	<p>4.6</p>
<p>Evidence for cost effectiveness</p>		
<p>Availability and nature of evidence</p>	<p>The committee accepted the structure of the company's economic model and considered it appropriate for decision-making. The company used efficacy data from KEYNOTE-024.</p>	<p>4.8 to 4.13</p>

<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>There are 3 main sources of uncertainty in the model:</p> <ul style="list-style-type: none"> • Treatment duration: the ICER increased as the maximum time on treatment increased. • Extrapolation of overall survival in KEYNOTE-024: the most appropriate method of overall survival extrapolation is hard to determine. The committee concluded that all time points presented for extrapolation (22-, 14- and 30-weeks) are equally plausible. • Utilities: utilities for long-term survivals derived from KEYNOTE-024 are implausibly high, and simply adjusting utilities to the population norm is still a conservative assumption. 	<p>4.9 to 4.15</p>
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<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>Accounting for the uncertainty in the utility values, the committee concluded that that the ICER would likely fall between that from the analysis setting the utility for 360 days to death to that of the UK population norm and the analysis using utilities from the pemetrexed guidance. The committee concluded that pembrolizumab could be considered an important treatment option for this population, but there were no additional benefits that had not been captured in the economic analysis.</p>	<p>4.15, 4.17</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>N/A</p>	<p>–</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>The key drivers of cost effectiveness were extrapolation of overall survival in both the pembrolizumab and standard care arms, and utility values for long-term survivors.</p>	<p>4.10, 4.14</p>

<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The ICER range identified by the committee for its decision-making was £46,083 to £61,577. The committee was aware that there is a commercial access agreement for pemetrexed monotherapy maintenance if used after pemetrexed and cisplatin induction therapy (one of the treatments used in the standard care arm). Including the commercial access agreement in the company's model would further increase these ICERs. The committee considered that the ICER range on which it was basing its decision was associated with uncertainty which needed to be accounted for when making its judgement about the acceptability of pembrolizumab as an effective use of NHS resources.</p>	<p>4.16</p>
<p>Additional factors taken into account</p>		

<p>Patient access schemes (PPRS)</p>	<p>The pricing arrangement considered during guidance development was that the company (Merck, Sharp & Dohme) had agreed a patient access scheme with the Department of Health. This scheme would provide a simple discount to the list price of pembrolizumab with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS. The managed access agreement agreed between the company and NHS England will replace the patient access scheme.</p>	<p>2</p>
<p>End-of-life considerations</p>	<p>The committee concluded that pembrolizumab met the life expectancy and life extension criteria to be considered a life-extending, end-of-life treatment.</p>	<p>4.18</p>

<p>Equalities considerations and social value judgements</p>	<p>The committee was aware of a comment that the guidance assumes that all patients suitable for pembrolizumab will be suitable for combination doublet chemotherapy, but rates of treatment with platinum doublet chemotherapy drop significantly with age in the UK. The committee agreed that as there are no specific recommendations for subgroups based on a patient's suitability for treatment either with pembrolizumab or platinum doublet chemotherapy as a result of age. Any recommendation resulting from this appraisal will apply to all people so age, as defined by the Equalities Act, is not a relevant equalities issues.</p>	<p>—</p>
<p>Cancer Drugs Fund (CDF)</p>	<p>The committee concluded that pembrolizumab met the criteria to be considered for inclusion in the Cancer Drugs Fund, and recommended pembrolizumab as an option for use within the Cancer Drugs Fund.</p>	<p>4.20</p>

5 Implementation

- 5.1 When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, NHS England will make it available within the conditions of the managed access agreement. This means that, if a person has untreated stage IV metastatic PD-L1-positive non-small-cell lung cancer (and their tumours express PD-L1 with at least a 50% tumour proportion score and have no epidermal growth factor receptor- or anaplastic lymphoma kinase-positive mutations) and the doctor

responsible for their care thinks that pembrolizumab is the right treatment, it should be available for use, in line with NICE's recommendations 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](#)

- 5.2 Pembrolizumab has been recommended according to the conditions in the managed access agreement. This includes a commercial access agreement that makes pembrolizumab available to the NHS at a reduced cost. The financial terms of the agreement are commercial in confidence. Any enquiries from NHS organisations about the commercial access agreement should be directed to [NICE to add details at time of publication]

6 Recommendations for data collection

- 6.1 As a condition of the positive recommendation and the managed access arrangement, the company is required to collect efficacy data from the KEYNOTE-024 study.

7 Review of guidance

- 7.1 This guidance will be updated when the data collection period is concluded which is currently anticipated to be December 2017, when the results of KEYNOTE-024 are available. The process for exiting the Cancer Drugs Fund will begin at this point and the review of the NICE guidance will start.
- 7.2 As part of the managed access agreement, the technology will continue to be available via the Cancer Drugs Fund after the data collection period has ended and while the guidance is being reviewed. This assumes that the data collection period ends as planned and the review of guidance

follows the standard timelines described in the [addendum](#) to NICE's methods and processes when appraising cancer technologies.

Lindsay Smith
Chair, appraisal committee
March 2017

8 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.

Marcela Haasova

Technical lead

Fay McCracken

Technical adviser

Kate Moore

Project manager

ISBN: [to be added at publication]