NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

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

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using pembrolizumab in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using pembrolizumab in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 21 March 2017

Second appraisal committee meeting: 29 March 2017

Details of membership of the appraisal committee are given in section 6.

1 Recommendations

1.1 Pembrolizumab is not recommended, within its marketing authorisation, for untreated PD-L1-positive metastatic non-small-cell lung cancer in adults whose 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.

1.2 This guidance is not intended to affect the position of patients whose treatment with pembrolizumab was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were 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	Pembrolizumab is available at a cost of £2,630.00 per 100 mg vial (company submission). The company has agreed a patient access scheme with the Department of Health. If pembrolizumab had been recommended, 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.

3 Evidence

The appraisal committee (section 6) 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 adverse events that they find unpleasant. Symptoms such as breathlessness and cough are difficult to treat. The clinical experts explained that new treatments which offer survival benefits with less adverse events 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 covers 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. But 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's 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's 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 of care. Standard of 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 a treatment option for people who have already had treatment. The committee heard from the clinical experts that although the proportion of patients having a pemetrexed-containing regimen in KEYNOTE-024 was smaller than expected, they considered that the standard of 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 needed patients to have 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 with clinical practice in England. The committee therefore concluded that KEYNOTE-024 is 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 of 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 of care. 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 of 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 early at the second interim analysis to give patients in the standard of 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 of 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 remain uncertain. The committee agreed that the 2-stage crossover adjustment method was appropriate, and that any estimate of overall survival is 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 of 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 one assigned to the pembrolizumab arm had completed 2 years therapy. The committee heard from clinical experts that the optimal 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 optimal 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 from 2 years to 3, 4, 5, 10 years, up to a life-time duration. These analyses increased the company base-case incremental cost-effectiveness ratio (ICER) from £41,213 per quality-adjusted life year (QALY) gained to £51,925, £60,157, £65,955, £81,020, and £84,868 per QALY gained respectively. 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 of care arm). 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 in the scenario analyses. Both of the scenario analyses increased the company's 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 is no direct evidence of effect from any clinical trials and there is 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 has assumed a constant mortality rate for both pembrolizumab and standard care arms after week 22. This mortality rate is higher for standard care arm than pembrolizumab for the 20 year time horizon of the model and effectively means that pembrolizumab continues 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 was disappointed that the company had only modelled a constant mortality rate for pembrolizumab after week 22, as this was unlikely based on current clinical understanding of disease progression. It noted that the duration of continued of 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 1.0 at different timepoints to model stopping of the continued treatment effect. The committee agreed that based on the data available, the most appropriate method of overall survival extrapolation is hard to determine. 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 and that there is a high level of uncertainty around the extrapolation of overall survival data and the long-term treatment effect.

4.11 The committee understood that the company's overall survival projection for patients who had standard care was 1.9% of patients at 5 years. The ERG noted that National Lung Cancer Audit (NCLA) 2006-2010 data suggest that 5-year survival with stage IV ECOG performance status 0 to 1 NSCLC is 5% and other sources suggest it could be as high as 13%. The ERG highlighted that the NCLA dataset is a reliable source of evidence but not all patients had chemotherapy (which has been shown to

extend life), so the 5% estimate is likely to be an underestimate of the survival rate. The clinical experts suggested that most of the NCLA patients would have had some form of therapy and that the registry survival estimate of 5% is reasonable.The clinical experts also noted that a small population of patients with EGFR mutation-positive tumours have a better survival prognosis, and if the data included any patients with EGFR mutation-positive tumours, the survival estimates may be higher compared with patients without the same mutation. The ERG and clinical experts agreed that the 5% survival rate at 5 years was the most plausible estimate of overall survival for patients with untreated stage IV metastatic PD-L1-positive NSCLC, but this still represent an understestimate because some patients did not receive chemotherapy. The committee noted that in the ERG's exploratory analyses, survival rates of 5% and 13% at 5 years in the standard of care arm were examined. These increased the company's base case ICER from £41,213 to £48,878 and £82,198 per QALY gained, respectively. The committee was mindful that that the company's overall survival projection of 1.9% at 5 years for the standard care arm was an underestimate and 13% at 5 years may be an overestimate. It therefore concluded that the NCLA estimate of 5% at 5 years was reasonable for use in decision making but this may still represent a conservative assumption based on the evidence given.

Utility values

4.12 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 of 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 are 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 87% and 97% of patients in the standard care and pembrolizumab arms of KEYNOTE-024 were current or former smokers. It agreed with the ERG that the utility values appeared implausible and did not seem in line with the physical symptoms described by the patient experts. 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 considered the ERG's exploratory analyses in which utility values from NICE's technology appraisal guidance on pemetrexed for treating non-small-cell lung cancer were used instead, and where the utility values for at least 360 days to death were set to the UK population norm. The compay's base-case ICER increased from £41,213 per QALY gained to £42,152 and £49,247 per QALY gained for the UK population norm capped utilities and utility values from NICE's technology appraisal guidance on pemetrexed respectively. The ERG noted that the scenario with utility values from the NICE's technology appraisal guidance on pemetrexed did not use time to death utilities and therefore represents only an exploratory analysis. The committee agreed that even 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. The committee concluded that while the ERG's exploratory analysis with the utility value for at least 360 days to death set to the UK population norm was the most plausible scenario of those presented, it still represented a conservative assumption based on the evidence given; the true utility value may lie

somewhere between that and the utility values from NICE's technology appraisal guidance on pemetrexed.

Most plausible ICER

4.13 The committee discussed the most plausible ICER for pembrolizumab compared with the standard of care. It noted that when applying its preferred assumptions of those presented; the 2 year stopping rule (see section 4.9), 5% survival at 5 years for the standard of care arm (see section 4.11), and a utility value for at least 360 days to death set at the UK population norm value (see section 4.12), this resulted in ICER of £50,028 per QALY gained. The committee was aware of its earlier conclusions. These were that setting the utility to the UK population norm (see section 4.12) and using the 5% overall survival estimate at 5 years from the standard care arm (see section 4.11) were conservative assumptions, and that the size of the overall survival gain for pembrolizumab is highly uncertain (see section 4.6). It was also 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 of care arm). Including the commercial access agreement in the company's model would further increase the ICERs presented here. Acknowledging the uncertainties in the clinical- and cost-effectiveness evidence, the committee concluded that the most plausible ICER for pembrolizumab compared with standard of care cannot be identified. But the committee was confident that the most plausible ICER for pembrolizumab compared with standard of care was in excess of £50,000 per QALY gained, and this was higher than the range usually considered a cost-effective use of NHS resources.

Innovation

4.14 The committee considered the innovative nature of pembrolizumab. It heard from the patient and clinical experts that there have been few

improvements for untreated metastatic NSCLC in people whose tumours have no EGFR- or ALK-positive mutations in the last 20 years, 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

4.15 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's final 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 months compared with 14.6 months for standard care. Therefore pembrolizumab may offer, on average, at least 3 months extension to life compared with the standard of care. But, 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, and 4.11). 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 could plausibly meet the criteria to be considered a life-extending, end-of-life treatment.

4.16 The committee concluded that because the estimates of overall survival were based on immature data, it could not be satisfied that the estimates of extension to life were sufficiently robust, and the uncertainty in the clinical- and cost-effectiveness data was too great. It could therefore 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

4.17 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 randomized, open label, phase III study of overall survival comparing pembrolizumab versus platinum based chemotherapy in treatment naïve subjects with 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. But, the most plausible ICER for pembrolizumab was higher than the range usually considered a cost-effective use of NHS resources and therefore did not have plausible potential for satisfying the criteria for routine use (see sections 4.13 and 4.16). The committee concluded that pembrolizumab did not satisfy the criteria to be considered for use in the Cancer Drugs Fund.

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 not recommended, within its marketing authorisation, for untreated PD-L1-positive metastatic non-small-cell lung cancer in adults whose tumours express PD-L1 with at least a 50% tumour proportion score and who have no epidermal growth factor receptor I or anaplastic lymphoma kinase-positive mutations. 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 of care, the exact size of the overall survival gain was uncertain because of the immaturity of the data. Acknowledging the uncertainties in the clinical- and cost-effectiveness evidence, the committee concluded that the most plausible ICER for pembrolizumab compared with standard of care cannot be identified. But the committee was confident that the most plausible ICER for pembrolizumab compared with standard of care was in excess of £50,000 per QALY gained, and this was higher than the range usually considered a cost-effective use of NHS resources.		1.1, 4.6, 4.13
Current practice		

Clinical need of patients, including the availability of alternative treatments	People with untreated metastatic non-small-cell lung cancer (NSCLC) whose tumours express at least 50% PD-L1 and who have no epidermal growth factor receptor (EGFR)- or anaplastic lymphoma kinase (ALK)-positive tumour mutations have limited treatment options. 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.	4.1, 4,3
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	People with NSCLC can have debilitating symptoms, and improving quality of life is important to this patient group. Pembrolizumab is generally well tolerated and has an important extension-to-life benefit for people with untreated metastatic PD-L1-positive NSCLC compared with standard of care.	4.1, 4.5

What is the position of the treatment in the pathway of care for the condition?	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. 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.	4.2, 4.3
Adverse reactions	Pembrolizumab is generally well tolerated.	4.1
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The clinical-effectiveness evidence for pembrolizumab came from KEYNOTE-024. This was an open label, phase III randomised controlled trial comparing pembrolizumab with standard of care arm (platinum-based combinations with either gemcitabine or paclitaxel, and a platinum-based combination with pemetrexed).	4.4
Relevance to general clinical practice in the NHS	The committee concluded that KEYNOTE-024 is generalisable to clinical practice in England.	4.4

Uncertainties generated by the evidence	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 of care, the exact size of the overall survival gain was uncertain because of the immaturity of the data. The committee concluded that limiting pembrolizumab treatment to 2 years is clinically plausiblebut that the optimal treatment duration is unknown.	4.6, 4.7
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	No clinically relevant subgroups were identified.	-
Estimate of the size of the clinical effectiveness including strength of supporting evidence	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 of care, the exact size of the overall survival gain was uncertain because of the immaturity of the data.	4.6
Evidence for cost effectiveness		

Availability and nature of evidence	The committee accepted the structure of the economic model developed by the company and considered it appropriate for decision-making. The company used efficacy data from KEYNOTE-024.	4.8-4.11

Uncertainties around and plausibility of assumptions and inputs in the economic model	There are 3 main sources of uncertainty in the model: • Treatment duration: The committee noted that the incremental cost-effectiveness ratio (ICER) increased as the proportion of patients having treatment after 2 years increased. • Extrapolation of overall survival in KEUNOTE-024: The ERG noted that by using an exponential distribution for overall survival extrapolation the company has assumed a constant mortality rate for both pembrolizumab and standard care arms after week 22. This mortality rate is higher for standard care arm than pembrolizumab for the 20 year time horizon of the model and effectively means that pembrolizumab continues 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 agreed that based on the data available, the most appropriate method of overall survival extrapolation is hard to determine. 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 and that there is	4.9, 4.11, 4.12

	a high level of uncertainty around the extrapolation of overall survival data and the long-term treatment effect. • Utilities: The evidence review group (ERG) highlighted that the utilities derived from KEYNOTE-024 are implausibly high (the values at 360 days before death were higher than the UK population norm for people of the same age). The committee agreed that the utility values appeared implausible and did not seem in line with the symptoms described by the patient experts. The committee agreed that given the clear physical and psychological symptoms reported by patients with NSCLC, simply adjusting utility to the population norm, the committee preferred utility assumption, would still be a conservative assumption.	

Incorporation of health-related quality-of-life benefits and utility values 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?	The committee concluded that the KEYNOTE-024 utility data (with the utility value for at least 360 days to death set to the UK population norm) were appropriate to inform decision-making, but still represented a conservative assumption based on the evidence given. The committee concluded that pembrolizumab addresses an unmet need in a debilitating condition, for which few treatment options are available, but there were no other health benefits not captured in the quality-adjusted life years (QALY).	4.12, 4.14
Are there specific groups of people for whom the technology is particularly cost effective?	No.	-

What are the key drivers of cost effectiveness?	The key drivers of cost-effectiveness were: • Extrapolation of overall survival in pembrolizumab arm: The committee agreed that based on the data available, the most appropriate method of overall survival extrapolation is hard to determine. 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 and that there is a high level of uncertainty around the extrapolation of overall survival data and the long-term treatment effect. • Extrapolation of overall survival in standard care arm: The committee was mindful that that the company's overall survival projection of 1.9% at 5 years for the standard care arm was an underestimate and 13% at 5 years may be an overestimate. It therefore concluded that the NCLA estimate of 5% at 5 years was reasonable for use in decision making but this may still represent a conservative assumption based on the evidence given. • Utility values for long-term survivors. The committee concluded that the KEYNOTE-024 utility data (with the utility value for at least 360 days to death set to the UK	4.10, 4.11, 4.12

	population norm) represented a conservative assumption based on the evidence given.	
Most likely cost-effectiveness estimate (given as an ICER)	The ICER of £50,028 per QALY gained for pembrolizumab compared with the standard of care, represented a conservative estimate. The committee was also aware that there is a commercial access agreement for pemetrexed monotherapy maintenance and that including this agreement in the company's model would further increase the ICER. Acknowledging the uncertainties in the clinical- and cost-effectiveness evidence, the committee concluded that the most plausible ICER for pembrolizumab compared with standard of care cannot be identified. But the committee was confident that the most plausible ICER for pembrolizumab compared with standard of care was in excess of £50,000 per QALY gained, and this was higher than the range usually considered a cost-effective use of NHS resources.	4.13
Additional factors taken into account		

Patient access schemes (PPRS)	The company has agreed a patient access scheme with the Department of Health. If pembrolizumab had been recommended, the scheme would provide a simple discount to the list price of pembrolizumab with the discount applied at the point of purchase or invoice. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.	2
End-of-life considerations	The committee considered that because of the immaturity of KEYNOTE-024 data, any estimate of an overall survival gain 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.	4.15
Equalities considerations and social value judgements	No equalities issues were raised during this appraisal.	–
Cancer Drugs Fund (CDF)	The committee agreed that pembrolizumab did not have the plausible potential for satisfying the criteria for routine use and concluded that pembrolizumab did not meet the criteria to be considered for use in the Cancer Drugs Fund.	4.18

5 Proposed date for review of guidance

5.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 2 years after publication of the guidance when the KEYNOTE-42 and the updated KEYNOTE-24 trial data are available. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Lindsay Smith
Chair, appraisal committee
February 2017

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.

Marcela Haasova
Technical Lead

Fay McCracken
Technical Adviser

Kate Moore
Project Manager

ISBN: [to be added at publication]