NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy

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: 24 October 2016

Second appraisal committee meeting: 26 October 2016

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 treating locally advanced or metastatic non-small-cell lung cancer in adults whose tumours express PD-L1 and who have had at least one prior chemotherapy regimen (and targeted treatment if they have an epidermal growth factor receptor [EGFR]- or anaplastic lymphoma kinase [ALK]-positive tumour).

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 ligand 1' protein (PD-L1). The PD-L1 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 treating locally advanced or metastatic non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 and who have had at least 1 chemotherapy regimen. Patients with epidermal growth factor receptor (EGFR)- or anaplastic lymphoma kinase (ALK)-positive tumour mutations should also have had approved therapy for these mutations before having pembrolizumab.
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	2 mg/kg every 3 weeks by intravenous (IV) infusion.
Price	£1,315.00 per 2 mg/kg dose administered as a 30-minute IV infusion every 3 weeks (excluding VAT; MIMS online and 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 discount to the list price of pembrolizumab 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 (ERG). 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 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 noted that people with locally advanced or metastatic NSCLC that has progressed after platinum based chemotherapy have a poor prognosis. It is a debilitating condition with many distressing symptoms. The committee heard from clinical experts that people with this condition have limited treatment options and that existing treatments such as docetaxel can cause severe adverse effects. It heard from the experts that premedication is not needed before pembrolizumab. The committee noted that pembrolizumab was better tolerated than docetaxel although a small proportion of people have immune-related adverse effects such as rash and colitis. The committee heard from the clinical experts that some people whose disease progresses rapidly after initial treatment or who cannot tolerate docetaxel currently have best supportive care and pembrolizumab may be considered suitable for these patients. The committee was aware that in their submissions the patient experts stated that the current outlook for patients with NSCLC whose disease has relapsed after platinum-based chemotherapy is poor. They noted that improving quality of life and even small extensions in duration of life are of considerable importance to this patient group. The committee concluded that pembrolizumab is an important treatment option for people with locally advanced or metastatic NSCLC whose tumours express PD-L1 and who have had platinum-based chemotherapy, and a targeted

treatment if the person has an epidermal growth factor receptor tyrosine kinase (EGFR-TK)- or anaplastic lymphoma kinase (ALK)-positive tumour.

4.2 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 the clinical experts that trial evidence suggested that the higher the level of PD-L1 expression, the greater the clinical response in people with locally advanced or metastatic NSCLC. The committee also heard from the clinical experts that because pembrolizumab is given by intravenous infusion every 3 weeks for 2 years, and for potentially longer than 2 years in some patients, this could increase pressure on current services. The clinical experts also noted that although PD-L1 testing is not part of standard NHS clinical practice, it is a straightforward immunohistochemical assay. It could be standardised quickly and, with training, quickly implemented as standard practice in the NHS. The clinical experts highlighted that re-biopsy on progression is becoming standard practice in lung oncology, but that re-biopsies for analysis of PD-L1 expression may not always be needed because testing of stored samples is possible. The committee noted that the costs of testing for PD-L1 expression were included in the company's economic analysis. The committee concluded that PD-L1 testing could be standardised quickly and, with training, quickly implemented as standard clinical practice in the NHS.

4.3 The committee discussed the clinical management of locally advanced or metastatic NSCLC. It understood from a clinical expert that platinum therapy is given as a first treatment for NSCLC in people whose tumours are not EGFR-TK-positive, followed by docetaxel or docetaxel plus nintedanib (depending on tumour histology). The committee understood that pembrolizumab would be considered as an option at this point in the treatment pathway. For people with EGFR-TK-positive tumours, treatment

starts with a tyrosine kinase inhibitor, followed by a platinum therapy option. For people with ALK-positive tumours, platinum combination therapy followed by an ALK inhibitor are the standard treatment choices. The committee heard from the clinical experts that pembrolizumab would be an alternative to docetaxel or to docetaxel plus nintedanib (depending on tumour histology) in people who have had targeted treatment for EGFR-TK- or ALK-positive tumours. The committee agreed with the company's approach of not comparing pembrolizumab with nivolumab, ceritinib or ramucirumab, which are the subject of NICE appraisals. The committee noted that the company had not compared pembrolizumab with best supportive care. It concluded that for a small proportion of patients who declined docetaxel, or could not tolerate it, best supportive care could be a relevant comparator but there was no direct evidence for this comparison. The committee also concluded that pembrolizumab was appropriately positioned in the clinical pathway as a treatment option for people who have had 1 prior chemotherapy regimen or prior chemotherapy plus a targeted therapy and as an alternative to docetaxel or to docetaxel plus nintedanib.

Clinical effectiveness

4.4 The committee noted that the clinical effectiveness evidence for pembrolizumab compared with docetaxel came from 3 studies:

- KEYNOTE-01
- KEYNOTE-010 and
- LUME-LUNG-01.

The committee considered that the KEYNOTE-010 evidence was the most applicable to the decision problem because the population was adults with PD-L1-positive locally advanced or metastatic NSCLC. The committee understood from the company submission that the trial was designed to assess the efficacy and safety of pembrolizumab in patients

with advanced PD-L1-positive NSCLC in 2 populations according to tumour proportion score (TPS), that is, the overall population with TPS greater than 1% and a population with TPS greater than 50%. The committee heard from the company that KEYNOTE-010 was powered to detect a difference between pembrolizumab and docetaxel in the population with TPS greater than 50% and in the overall TPS greater than1% population, but not for the TPS 1–49% population. The committee heard from the clinical experts that the overall population in KEYNOTE-010 was likely to be the same as those who have pembrolizumab in clinical practice. The committee concluded that the population in KEYNOTE-010 was generalisable to clinical practice in England.

4.5 The committee noted that the median overall survival gain from KEYNOTE-010 was 10.4 months for pembrolizumab compared with 8.5 months for docetaxel in the intention-to-treat population. This difference was statistically significant. Based on the 30 September 2015 data cut, the median duration of follow-up for KEYNOTE-010 was 13 months (range 6 to 24 months). The committee concluded that based on the trial data, pembrolizumab had an important extension-to-life benefit for people with locally advanced or metastatic NSCLC whose tumours express PD-L1 compared with docetaxel.

4.6 The committee discussed the network meta-analysis presented by the company, which compared the relative treatment effects of pembrolizumab with nintedanib plus docetaxel in the population with adenocarcinoma. Two studies formed the basis of the indirect treatment comparison: KEYNOTE-010 and LUME-LUNG-01. Both trials included docetaxel as a comparator, forming a network. LUME-LUNG-01 included adults with advanced NSCLC whose disease had progressed on or after treatment with only 1 prior chemotherapy regimen. This study included patients with adenocarcinoma (approximately 50% of the study population). The evidence review group (ERG) stated that the network

meta-analysis was limited because it only included 2 studies, the trial populations were very different and the results should be interpreted with caution. The ERG highlighted that KEYNOTE-010 included adults with PD-L1-positive advanced NSCLC whose disease has progressed after targeted therapy for EGFR- or ALK-positive tumours. But in LUME-LUNG-01, neither PD-L1 expression nor EGFR mutation status was assessed in the patients with advanced NSCLC. The committee noted that the results from the network meta-analysis were not directly used in the economic model. Only the hazard ratio for nintedanib plus docetaxel compared with docetaxel was applied to the docetaxel arm in the model for the adenocarcinoma subgroup. The committee concluded that the network meta-analysis was not robust, and that the trial populations of KEYNOTE-010 and LUME-LUNG-01 were too different. Therefore it was not appropriate for decision-making regarding the relative effectiveness of pembrolizumab compared with nintedanib in the population with adenocarcinoma histology.

Cost effectiveness

4.7 The committee discussed the cost-effectiveness evidence presented by the company and its critique by the ERG. It accepted the structure of the economic model developed by the company and considered it appropriate for decision-making.

Treatment duration

4.8 The committee discussed the assumption in the company's model that at 2 years all patients whose disease had not progressed (the pre-progression state) would stop treatment. It understood that this assumption was based on the KEYNOTE-010 protocol, which stated that patients could continue pembrolizumab until disease progression or unacceptable toxicity, or for 2 years without interruption. The committee recalled that the company's submission stated that the optimal duration of treatment with pembrolizumab is unknown. It was aware of the clinical

experts' comments that this is because the data are immature. The committee heard from the company that based on the latest cut-off data set (31 March 2016) and additional follow-up data (to 21 July 2016) no KEYNOTE-010 patients continued treatment after 2 years. In line with the protocol, patients discontinued treatment after 2 years of uninterrupted therapy (and no documented disease progression) or 35 treatment administrations, whichever occurred later. The committee considered the company's analyses exploring the effect of varying the proportion of patients having treatment after 2 years and before disease progression. It noted that the incremental cost-effectiveness ratio (ICER) increased as the proportion of patients having treatment after 2 years increased. The committee noted that, despite being in the trial protocol, there is no 2-year stopping rule in the pembrolizumab summary of product characteristics. The clinical experts stated that in clinical practice, the decision to stop treatment would be agreed between the clinician and the patient, but the number of patients likely to have treatment after 2 years would be small. The clinical experts also stated that patients who stopped treatment would be followed up with the possibility of restarting treatment depending on the clinical circumstances. The committee noted the uncertainty around the optimal duration of treatment and was aware that it had not been presented with compelling evidence that a 2-year stopping rule would be applied in clinical practice. The committee concluded that for the base case, all people having pembrolizumab would continue treatment after 2 years if their disease had not progressed.

Treatment switching

4.9 The committee heard that crossover was not permitted in KEYNOTE-010. However, the company reported that of the patients randomised to chemotherapy, 48% (50 people) crossed over and had treatment with pembrolizumab or other anti-PD-L1 treatments after treatment discontinuation. A 2-stage adjustment method was used by the company to account for treatment switching in the base case analyses. The rank-

preserving structural failure time (RPSFT) method, a pre-specified analysis was presented as a scenario. The committee noted that the ICER for pembrolizumab compared with docetaxel was higher than that for the 2-stage method. The committee heard from the ERG that the RPSFT method does not have a test for a common treatment effect and it preferred the 2-stage adjustment method to account for the effects of crossover; it also noted that this method has been used in other appraisals of immunotherapies. The committee noted that the adjustment method for treatment switching has a large effect on projecting mean overall survival in the model. The committee concluded that the most appropriate method to adjust for treatment switching was unclear but the 2-stage adjustment method was reasonable.

Time on treatment and additional weeks of therapy

4.10 The committee discussed time on treatment for people enrolled in KEYNOTE-010. The ERG highlighted that when using the individual patient level data provided by the company at clarification stage, the ERG analyses gave an estimated treatment duration of 217 days using the gamma model and 255 days with the Kaplan–Meier plus exponential model (base case 2). The company also did analyses in which different parametric curves were fitted. It concluded that the generalised gamma model did not provide the best model or visual fit. The committee noted that it would have preferred to see time on treatment taken directly from KEYNOTE-010 rather than the company's approach of using time to progression with a constant hazard adjustment to estimate time to treatment discontinuation. The committee was not clear about how many patients had scans to check for true disease progression and what proportion of these scans confirmed disease progression. The committee noted that additional weeks of therapy were sometimes needed (as stated in the KEYNOTE-010 protocol) to distinguish between true progression and pseudo-progression. Pseudo-progression is when tumours appear to enlarge but then respond to treatment. It heard from the clinical experts

that additional outpatient visits and CT scans may be needed for approximately 10% of patients in clinical practice. In response to a query from committee, the company clarified that the hazard ratio for the relationship between disease progression and time on treatment (HR=1.039) included administration costs for people who remained on pembrolizumab (needing a confirmatory scan) and people whose disease had not yet progressed. The company did not specifically adjust for pseudo-progression in their estimates of treatment costs, but the committee heard from the company that if patients remained on treatment during pseudo-progression, the time on treatment data would reflect this. The ERG stated that, overall, the adjusted progression-free survival curve appeared very similar to the time on treatment curve. However, the committee noted that after a confirmatory scan some patients remained on treatment after disease progression. It was unclear if some patients, who did not need a scan to confirm true progression, continued therapy in the progressed state. The committee concluded that there was still some uncertainty about how many people continue treatment after disease progression and noted that these treatment and administration costs may not be appropriately captured in the company analyses presented.

Extrapolation methods used for overall survival

4.11 The committee noted that, to estimate overall survival, the company used 52-week Kaplan–Meier data from KEYNOTE-010. After 52 weeks, for docetaxel, the company fitted an exponential model to the KEYNOTE-010 data after a 2-stage crossover adjustment. For pembrolizumab, after 52 weeks the company fitted an exponential model to the KEYNOTE-01 data (base case 1) and to the KEYNOTE-010 data (base case 2). The committee heard that the ERG preferred base case 2 because it considered that base case 1 had internal validity problems. The ERG also noted that KEYNOTE-010 was a better source of evidence than KEYNOTE-01. They noted the KEYNOTE-010 population consisted of people with PD-L1 positive NSCLC only whilst KEYNOTE-01

retrospectively identified for PD-L1. The committee concluded that base case 2 was most appropriate for decision-making.

4.12 The committee discussed the different cut-off points used when switching from trial survival data to the exponential survival modelling. The company explored cut-off points of 42, 62, 72 and 82 weeks as well as 52 weeks. The committee discussed the effect of changing the cut-off points in the sensitivity analyses on the cost-effectiveness results. It understood that the company fitted the exponential model to the data from 52 weeks onwards and applied the same exponential curve to the Kaplan–Meier data at the different time points. The committee understood from the company that the 52-week cut-off point was considered logical because of the inflection in the survival data at that point. The ERG commented that this inflection is a result of the modelling approach that treats the timing of deaths up to 52 weeks as being unrelated to the timing of deaths beyond 52 weeks. The ERG added that the inflection in the Kaplan–Meier trial survival data was less pronounced in the more recent data cut from March 2016. The committee noted that the company had asked external health economic experts about selecting a cut-off point from the Kaplan–Meier curve to switch to the exponential curve for overall survival. There was agreement between the committee and ERG that there was no clear choice of cut-off point that could be easily justified from the data available, and that other cut-off points should also be explored. Using the individual patient data from the company, based on its original approach, the ERG re-estimated the exponential curve for each different cut-off point on the survival curve. The committee noted the marked sensitivity of the ICER to the choice of different cut-off points when using the company and the ERG's approach to deriving the exponential curve. The company stated that the 52-week cut-off for extrapolation was a conservative estimate. The committee considered the ERG's review of the relationship between the estimated hazard ratio from its analysis and long-term extrapolation using different cut-off points from the trial survival data. This highlighted

that the hazard ratio was sensitive to the choice of cut-off point. At 52 weeks the long-term hazard ratio is 0.35, giving an improvement in overall survival (undiscounted) of 0.92 years. In contrast, if the analysis is repeated with a hazard ratio of 1, representing no long-term incremental effect on survival, the incremental overall survival would be 0.18 years. In the company submission a scenario was presented in which a 62-week extrapolation was used and the ICERs were lower than at 52 weeks. However, the committee felt that having a lower ICER for a 62-week cut-off compared with a 52-week cut-off when using the same exponential extrapolation was illogical. The committee agreed with the company that using cut-off points beyond 62 weeks may be unreliable because there are few patients who remain at risk, resulting in a flat extrapolation of overall survival. The committee also heard from the clinical experts that for checkpoint inhibitors such as pembrolizumab there is no specific biological basis for choosing a 52-week cut-off point compared with other time points. The committee concluded that there was no evidence that the 52-week cut-off was the most appropriate for extrapolating the Kaplan–Meier data and that the ICER was very sensitive to the cut-off point chosen to model overall survival. The committee concluded that the choice of the 52-week cut-off point was overly optimistic.

Long-term treatment effect

4.13 The committee understood that the company's survival estimates in base case 2 depend on an ongoing reduction in the risk of death with pembrolizumab (time to death was independent of previous time on treatment or disease progression) for those who survive, which continues after treatment has stopped and is maintained for a lifetime. The committee recalled that the modelling projections used by the company suggested that 12% of patients in the pembrolizumab arm would be alive at 5 years and agreed with the experts that this was extremely optimistic, as was the assumption of no waning of treatment effect over 20 years irrespective of the time spent on treatment or disease progression. The

company modelled a scenario in which there was a waning of the treatment effect over time once treatment had stopped after 2 years. The committee noted that the ICER increased with waning of the treatment effect. The ERG explored a different method to extrapolate the continuing benefit of pembrolizumab after treatment had stopped, at different time points over the lifetime of the model. The committee noted the effect at 3, 5 and 10 years, which showed that the treatment effect duration would need to last at least 10 years for pembrolizumab to be considered cost effective, at a willingness to pay threshold of £50,000 per quality-adjusted life year (QALY) gained, when using all of the committee's preferred assumptions. The committee noted the ERG presented data from Schadendorf (2015). This was a meta-analysis of studies in which patients received ipilimumab for treating unresectable or metastatic melanoma. The committee considered that although it is likely there would be some continued benefit of pembrolizumab after stopping treatment and in the progressed state, the size of this effect and its duration is unknown for NSCLC. The committee concluded that the ICERs were highly sensitive to a continued treatment effect after stopping treatment, and the company's additional analyses on the continued treatment effect represented the most optimistic modelling scenario presented.

Utility values used in the pre- and post-progression states

4.14 The committee concluded that the KEYNOTE-010 utility data were the most appropriate to inform decision-making and including a disutility for adverse events was appropriate.

Most plausible ICER

4.15 The committee discussed the most plausible ICER for pembrolizumab compared with docetaxel. It noted comments from the clinical experts that the appropriate population is the overall population expressing PD-L1. Also, the committee considered that the indirect comparison in the adenocarcinoma subgroup was too unreliable for decision-making and so

it focused on the pembrolizumab and docetaxel comparison in the overall population. The committee agreed that the KEYNOTE-010 data used in base case 2 were more appropriate, compared with the KEYNOTE-01 data used in base case 1. The committee's starting point for identifying the most plausible ICER was the company's base case 2 probabilistic ICER of £46,148 per QALY gained. This assumed: 25% of patients still on treatment at 2 years would continue; a 2-stage cross-over adjustment for treatment switching; used progression-free survival and hazard ratio adjustment to estimate time on treatment; a 52-week cut-off point for survival extrapolation; treatment benefit continued after treatment had stopped, post-progression based utilities from KEYNOTE-010; and included adverse event related disutility. The committee was aware of its earlier conclusions: all patients who continue to benefit would continue pembrolizumab beyond 2 years, which would increase the ICER by approximately £4,000; the ICER would also be likely to increase if a different extrapolation cut-off point is used and when any waning of continued treatment effect after treatment stops is included. The committee noted the ERG's preferred scenario, which used the company's base case assumptions but which stopped the treatment effect for pembrolizumab at 3 years. This resulted in an ICER of £65,200 per QALY gained for pembrolizumab compared with docetaxel. Acknowledging the uncertainties in the clinical and cost-effectiveness evidence, the committee concluded that the most plausible ICER for pembrolizumab compared with docetaxel would exceed £50,000 per QALY gained.

4.16 The committee heard from the clinical and patient 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 compared with docetaxel, is easy to administer and shows an improvement in overall survival benefit compared with available agents. 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 benefits not captured in the QALY.

End-of-life considerations

4.17 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. It noted the evidence presented by the company, which showed that people with NSCLC have a life expectancy of less than 24 months. The committee heard that the average number of months of life gained with pembrolizumab, as estimated by the company's economic model, is between 21.2 and 22.8 months, compared with 10.4 months with docetaxel. It agreed that there is significant uncertainty in the overall survival gain and that this degree of benefit is likely to be optimistic. However, the committee considered it reasonable to assume that the benefit is likely to exceed 3 months. The committee therefore concluded that pembrolizumab met the end-of-life criteria and that it can be considered a life-extending, end-of-life treatment.

4.18 The committee concluded that the most plausible ICER for pembrolizumab was higher than the range usually considered a cost-effective use of NHS resources, even when considering that pembrolizumab is a life-extending, end-of-life treatment.

4.19 The committee discussed the new arrangements for the Cancer Drugs Fund recently agreed by NICE and NHS England, noting the addendum to the NICE process and methods guides. Given the conclusion in section 4.18, the committee agreed that pembrolizumab did not have the plausible potential for satisfying the criteria for routine use. As the first criteria for use in the CDF has not been met, the committee did not need to further conclude on the data collection criterion. The committee concluded that

pembrolizumab did not meet the criteria to be considered for use in the Cancer Drugs Fund.

Summary of appraisal committee's key conclusions

TAXXX	Appraisal title: Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy	Section
Key conclusion		
Pembrolizumab is not recommended, within its marketing authorisation, for treating locally advanced or metastatic non-small-cell lung cancer (NSCLC) in adults whose tumours express PD-L1 and who have had platinum-based chemotherapy (and targeted treatment if they have an epidermal growth factor receptor [EGFR]- or anaplastic lymphoma kinase [ALK]-positive tumour).		1.1, 4.18
The committee concluded that pembrolizumab had an important extension-to-life benefit for people with locally advanced or metastatic NSCLC whose tumours express PD-L1 based on the KEYNOTE-010 trial data.		4.5
The committee concluded that all patients who continue to benefit would continue pembrolizumab beyond 2 years, which would increase the incremental cost-effectiveness ratio (ICER). The ICER would also increase if a different extrapolation cut-off point is used and when any waning of continued treatment effect after treatment stops is included.		4.15
The committee concluded that the most plausible ICER for pembrolizumab was higher than the range usually considered a cost-effective use of NHS resources, even when considering that pembrolizumab is a life-extending, end-of-life treatment.		4.18
Current practice		

Clinical need of patients, including the availability of alternative treatments	People with locally advanced or metastatic NSCLC have a poor prognosis. It is a debilitating condition with many distressing symptoms. Improving quality of life and even small extensions in duration of life are of considerable importance to this patient group. Platinum therapy is given as a first treatment for NSCLC in people whose disease is not EGFR-TK-positive, followed by docetaxel or docetaxel plus nintedanib (depending on tumour histology).	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 have limited treatment options and existing treatments such as docetaxel can cause severe adverse effects. Premedication is not needed before pembrolizumab and it is generally well tolerated. Based on clinical trial data, pembrolizumab provides a statistically significant median overall survival gain compared with docetaxel and an important extension-to-life benefit for people with locally advanced or metastatic NSCLC whose tumours express PD-L1.	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	4.2

	validated test. The committee understood from a clinical expert that platinum therapy is given as a first treatment for NSCLC in people whose tumours are not EGFR-TK-positive, followed by docetaxel or docetaxel plus nintedanib (depending on tumour histology). For people with EGFR-TK-positive tumours, treatment starts with a tyrosine kinase inhibitor, followed by a platinum therapy option. For people with ALK-positive tumours, platinum combination therapy followed by an ALK inhibitor are the standard treatment choices. The committee heard from the clinical experts that pembrolizumab would be an alternative to docetaxel or to docetaxel plus nintedanib (depending on tumour histology) in people who have had targeted treatment for EGFR-TK- or ALK-positive tumours. The committee concluded that pembrolizumab was appropriately positioned in the clinical pathway as a treatment option for people who have had 2 or 3 therapies and as an alternative to docetaxel or to docetaxel plus nintedanib.	4.3
Adverse reactions	A small proportion of people have immune-related adverse effects such as rash and colitis.	4.1

Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The clinical evidence for treating NSCLC came from 3 studies (KEYNOTE-01, KEYNOTE-010 and LUME-LUNG-01). The committee considered that the KEYNOTE-010 evidence was the most applicable to the decision problem because the population was adults with PD-L1-positive locally advanced or metastatic NSCLC. The committee concluded that pembrolizumab had an important extension-to-life benefit for people with locally advanced or metastatic NSCLC whose tumours express PD L1 based on the trial data. The committee concluded that the network meta-analysis was not robust and was limited because of the differences between the trial populations. Therefore it was not appropriate for decision-making on the effectiveness of pembrolizumab in the population with adenocarcinoma histology.	4.4 4.4, 4.11 4.5 4.6
Relevance to general clinical practice in the NHS	KEYNOTE-010 evidence was the most applicable to the decision problem because the population was adults with PD-L1-positive locally advanced or metastatic NSCLC.	4.4
Uncertainties generated by the	The committee noted the uncertainty around the optimal duration of treatment and was	4.8

evidence	aware that it had not been presented with compelling evidence that a 2-year stopping rule would be applied in clinical practice. The committee noted that the adjustment method for treatment switching has a large effect on projecting mean overall survival in the model. The committee concluded that the most appropriate method to adjust for treatment switching was unclear but the 2-stage method was reasonable. The committee concluded that there was still some uncertainty about how many people continue treatment after disease progression and noted that these treatment and administration costs would not be included in the company analyses. The committee concluded that there was no evidence that the 52-week cut-off was the most appropriate for extrapolating the Kaplan–Meier data and that the ICER was very sensitive to the cut-off point chosen to model overall survival. The committee considered that although it is likely there would be some continued benefit of pembrolizumab after stopping treatment and in the progressed state, the size of this effect and its duration is unknown for NSCLC.	4.9 4.10 4.11 4.12

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The company presented a network meta-analysis to compare the relative treatment effects of pembrolizumab with nintedanib plus docetaxel in the population with adenocarcinoma. Two studies formed the basis of the indirect treatment comparison: KEYNOTE-010 and LUME-LUNG-01. The committee concluded that the network meta-analysis was not robust, and that the trial populations of KEYNOTE-010 and LUME-LUNG-01 were too different. Therefore it was not appropriate for decision-making on the effectiveness of pembrolizumab in the population with adenocarcinoma histology.	4.6
Estimate of the size of the clinical effectiveness including strength of supporting evidence	In the overall population in KEYNOTE-010 the median overall survival gain was 10.4 months for pembrolizumab compared with 8.5 months for docetaxel. The committee concluded that pembrolizumab had an important extension-to-life benefit compared with docetaxel.	4.5
Evidence for cost effectiveness		
Availability and nature of evidence	The commmittee accepted the structure of the economic model developed by the company and considered it appropriate for decision-making The company used efficacy data for pembrolizumab and docetaxel from KEYNOTE-010.	4.7, 4.10
Uncertainties around and plausibility of	The company's model assumed that at 2 years all patients whose disease had not	4.7, 4.9, 4.10,

assumptions and inputs in the economic model	progressed would stop treatment despite there being no stopping rule in the pembrolizumab marketing authorisation. The committee noted that it was not presented with compelling evidence that it would be applied in clinical practice. The committee was not clear about how many patients had scans to check for true disease progression and what proportion of these scans confirmed disease progression. The committee noted that additional weeks of therapy were sometimes needed (as stated in the KEYNOTE-010 protocol) to distinguish between true progression and pseudo-progression. The committee concluded that there was still some uncertainty about how many people continue treatment after disease progression and noted that these treatment and administration costs would not be included in the company analyses.	4.11
	The committee concluded that it preferred base case 2. It noted there was no evidence that the 52-week cut-off was the most appropriate for extrapolating the Kaplan–Meier data and that the ICER was very sensitive to the cut-off point chosen to model overall survival. The committee concluded that the choice of the 52-week cut-off point was overly optimistic.	

	The committee concluded that the ICERs were highly sensitive to a continued treatment effect after stopping treatment, and the company's analyses on the continued treatment effect represented the most optimistic modelling scenario presented.	
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-010 utility data were the most appropriate to inform decision-making and including a disutility for adverse events was appropriate. 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 QALY.	4.14 4.16
Are there specific groups of people for whom the technology is particularly cost effective?	No	–
What are the key drivers of cost	The key drivers of cost-effectiveness were: • Treatment duration: the committee noted	

effectiveness?	that the ICER increased as the proportion of patients having treatment after 2 years increased. • Extrapolation of overall survival: The committee noted the marked sensitivity of the ICER to the choice of different cut-off points when using the company and the ERG's approach to deriving the exponential curve. The committee concluded that there was no evidence that the 52-week cut-off was the most appropriate for extrapolating the Kaplan–Meier data and that the ICER was very sensitive to the cut-off point chosen to model overall survival. • Long-term treatment effect: The committee noted that the ICER increased with waning of the treatment effect. The committee concluded that the ICERs were highly sensitive to a continued treatment effect after stopping treatment, and the company's analyses on the continued treatment effect represented the most optimistic modelling scenario presented.	4.8 4.11, 4.12 4.13
Most likely cost-effectiveness estimate (given as an ICER)	The committee's starting point for identifying the most plausible ICER was the company's base case 2. The committee preferred the company's base case 2 probabilistic ICER of £46,148 per quality-adjusted life year (QALY) gained. The committee was aware of its earlier conclusions: all patients who continue to benefit would continue pembrolizumab	4.15,

	beyond 2 years, which would increase the ICER by approximately £4,000; the ICER would also be likely to increase if a different extrapolation cut-off point is used and when any waning of continued treatment effect after treatment stops is included. Acknowledging uncertainties in the clinical and cost-effectiveness evidence, the committee concluded that the most plausible ICER would exceed £50,000 per QALY gained.	
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 heard that people with NSCLC have a life expectancy of less than 24 months. The committee heard that the average number of months of life gained with pembrolizumab, as estimated by the company's economic model, is between 21.2 and 22.8 months, compared with 10.4 months with docetaxel. It agreed that there is	4.17

	significant uncertainty in the overall survival gain, and that this degree of benefit is likely to be optimistic. However it was reasonable to assume that the benefit is likely to exceed 3 months. The committee therefore concluded that pembrolizumab met the end-of-life criteria and that it can be considered a life-extending, end-of-life treatment.	
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.	4.19

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 3 years after publication of the guidance. 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.

Professor Gary McVeigh
Chair, appraisal committee
September 2016

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.

Stuart Wood
Technical Lead

Fay McCracken
Technical Adviser

Kate Moore
Project Manager

ISBN: [to be added at publication]