NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Nivolumab for previously treated locally advanced or metastatic non-squamous 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 nivolumab 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 nivolumab 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: 5pm, Friday 3 June 2016

Second appraisal committee meeting: Wednesday 15 June 2016

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

1 Recommendations

1.1 Nivolumab is not recommended for treating locally advanced or metastatic non-squamous non-small-cell lung cancer in adults whose disease has progressed after chemotherapy.

1.2 This guidance is not intended to affect the position of patients whose treatment with nivolumab 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

2.1 Nivolumab (Opdivo, Bristol–Myers Squibb) is a monoclonal antibody that targets a receptor on the surface of lymphocytes known as PD-1. This receptor is part of the immune checkpoint pathway, and blocking its activity may promote an anti-tumour immune response. Nivolumab has a marketing authorisation for treating 'locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy in adults'. Before the marketing authorisation was granted, nivolumab was available in the NHS through the Early Access to Medicines Scheme (EAMS). It is given intravenously, at a dose of 3 mg/kg body weight every 2 weeks.

2.2 The most common adverse reactions with nivolumab in clinical trials were tiredness, decreased appetite and nausea (occurring in more than 10% of people). The summary of product characteristics notes that nivolumab is most commonly associated with immune-related adverse reactions, including pneumonitis, colitis, hepatitis, nephritis and kidney dysfunction, endocrinopathies and rash. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Nivolumab is available at a list price of £439 per 40-mg vial (excluding VAT; company submission). This equates to an estimated cost of £31,960 for a course of treatment (assumes 12.6 doses on average). Costs may vary in different settings because of negotiated procurement discounts.

2.4 The company has agreed a patient access scheme with the Department of Health. If nivolumab had been recommended, this scheme would have provided a complex patient access scheme for nivolumab, under which the NHS would pay for each patient's treatment with nivolumab for up to 26 cycles. The cost of the drug for patients continuing treatment beyond 26 cycles would be covered by BMS. The proposed scheme would only apply to the NSCLC indications currently being appraised by NICE. 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 Bristol–Myers Squibb and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence. The clinical-effectiveness evidence base is in the company's evidence submission (pages 41–135) and the ERG report (pages 24–62), and is summarised in the clinical-effectiveness slides presented at the appraisal committee meeting. The cost-effectiveness evidence base is in the company's evidence submission (pages136–242), the appendices to the company's evidence submission and the ERG report (pages 63–121, and is summarised in the cost-effectiveness slides presented at the appraisal committee meeting.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of nivolumab, having considered evidence on the

nature of non-squamous non-small-cell lung cancer (NSCLC) and the value placed on the benefits of nivolumab by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1 The committee noted that non-squamous NSCLC causes debilitating and distressing symptoms and that it is often diagnosed late in life. The committee heard from clinical experts that people with this condition have limited treatment options and that existing treatment options are associated with high toxicity. It also heard from patient experts that chemotherapy is not well tolerated; any improvement in quality of life and extension to life would be a significant benefit for patients and their families.

4.2 The committee discussed the management of non-squamous NSCLC in clinical practice. It understood from a clinical expert that platinum therapy is given as a first treatment for NSCLC in people whose disease is not epidermal growth factor receptor (EGFR) positive. For those with EGFR-positive disease, treatment would start with a targeted tyrosine kinase inhibitor (TKI) such as erlotinib, followed by a platinum therapy option after the disease stops responding to TKI therapy. For those with anaplastic lymphoma kinase (ALK) positive NSCLC, platinum combination therapy followed by the targeted ALK-inhibitor crizotinib would be the standard treatment choices. The committee understood that the marketing authorisation for nivolumab for non-squamous NSCLC specifies that it is used after chemotherapy. So it agreed with the clinical expert and the company that in disease that is not genetic-mutation positive, nivolumab would be a second-line treatment option and that in genetic-mutation-positive disease (either EGFR or ALK positive) nivolumab would be a third-line treatment option. It confirmed with the clinical expert that in both the second- and third-line treatment setting, the comparators would be docetaxel, nintedanib plus docetaxel for people with adenocarcinoma, and

best supportive care (BSC) when docetaxel was not a suitable option. The committee was aware that the company had not provided comparisons with erlotinib or crizotinib, but considered this to be reasonable because these targeted agents would be given before nivolumab and would not be displaced if nivolumab were available in NHS clinical practice. The committee concluded that for the populations under consideration, the relevant comparators for this appraisal were nintedanib plus docetaxel, docetaxel monotherapy, and BSC.

Clinical effectiveness

The committee discussed the clinical evidence presented for nivolumab and its comparators. It noted that the company only presented clinical evidence for nivolumab compared with docetaxel, nintedanib plus docetaxel, and BSC.

4.3 The committee noted that the key clinical-effectiveness evidence for nivolumab compared with docetaxel came from the CheckMate-057 trial. This was an international, open-label, phase III randomised controlled trial, in adults with non-squamous NSCLC whose disease had progressed during or after 1 platinum doublet-based chemotherapy regimen. The committee noted that the trial had been stopped early, after the primary endpoint (overall survival) was met at the interim analysis in March 2015 (referred to as the 12-month interim analysis). The committee considered that the overall survival gain of 2.8 months for nivolumab compared with docetaxel, as reported in the 12-months analysis, was an important extension-to-life benefit for people with advanced NSCLC who have had chemotherapy. It also considered that this was supported by the results of the 18-months analysis (July 2015), which also showed a statistically significant overall survival benefit for nivolumab compared with docetaxel. The committee heard from the company that the mortality rate for nivolumab declined towards the end of the available trial data, suggesting a decreasing rate of deaths on nivolumab as time on treatment increases.

It heard from the company that this long-term survival benefit with nivolumab was plausible and consistent with 4-year data from the single-arm CheckMate-003 trial, which showed a 15% survival rate for the subgroup of people with NSCLC in the trial. The committee also heard from a clinical expert that a longer-term mortality benefit is consistent with what is seen in clinical practice and in their opinion it is likely to be due to the mechanism of action of nivolumab. In contrast, the committee heard from the ERG that the trial data did not support an increasing difference in the mortality rates in the last part of the overall survival data of nivolumab compared with docetaxel, and that from around 12 months this data settled to a phase of constant hazard (that is, the same mortality rate between the treatment groups). This was shown in the linear rise in cumulative hazard shown in figure 18 in the ERG report (see the committee papers). The committee considered this figure and was not persuaded that the trial data supported a decrease in the rate of mortality with nivolumab to the extent suggested by the company. It recognised that nivolumab, with a different mechanism of action, may produce a long-term overall survival benefit, although it considered that the single arm CheckMate-003 did not support this comparative advantage of nivolumab over docetaxel. The committee concluded that nivolumab is clinically effective and offers a gain in survival compared with docetaxel, and that the data do not show that a difference in mortality rate would persist beyond that observed in the trial.

4.4 The committee was aware of the evidence presented by the company for the comparison of nivolumab with nintedanib plus docetaxel and BSC. The committee heard from the clinical expert that complications with the combination treatment of nintedanib plus docetaxel are high and that the clinical benefit seen in NHS practice has been marginal. The clinical expert told the committee that BSC would not be expected to give as much of an extension to life as docetaxel, although the benefit of docetaxel over BSC is small. The committee was not presented with

conclusive evidence of the exact extent of survival or quality-of-life gain that nivolumab would offer compared with nintedanib plus docetaxel, or BSC. It noted the results of the indirect treatment comparison presented by the company and accepted the company and ERG's views that this was not a reliable estimate of comparative effectiveness. On the basis of the clinical and patient expert comments, the committee was persuaded that nivolumab would offer some quality-of-life benefit over nintedanib because it avoids the toxicity associated with docetaxel. It further concluded that it is reasonable to expect that nivolumab would offer at least the same survival gain over BSC as docetaxel, and that the quality-of-life gain may be higher due to the difficulties in tolerating docetaxel with the combination therapy.

4.5 The committee noted that the marketing authorisation for nivolumab does not specify PD-L1 mutation expression, nor was it required by the scope for the appraisal, however the clinical-effectiveness data for PD-L1 subgroups had been presented by the company (that is, PD-L1 expression of 1% or more, 5% or more, and 10% or more). It noted that the data showed that overall survival with nivolumab was greater for those subgroups in which the PD-L1 expression level was above 1%, 5% and 10% than in those with levels below these thresholds, suggesting that the higher the level of PD-L1 expression the more effective nivolumab becomes. Also, within these subgroups, both docetaxel and nivolumab seemed to offer similar overall survival benefit to people whose PD-L1 level was lower than the defined threshold of 1%, 5% or 10%. The committee was aware from the company that the trial was not powered to measure the benefit of nivolumab over docetaxel at different PD-L1 levels. It also heard from the clinical expert that nivolumab still offers a clinical benefit for people with low-level or no PD-L1 expression, because docetaxel has a high level of toxicity and is difficult to tolerate. The committee recognised that there are difficulties with using PD-L1 for specifying a subgroup, and that the trial was not powered to analyse by

PD-L1 expression. However, it concluded that it could be plausible that nivolumab might have a different level of clinical effectiveness according to PD-L1 expression.

Cost effectiveness

4.6 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 went on to discuss some of the parameters and assumptions within the model.

4.7 The committee discussed the method used for extrapolating overall survival for comparing nivolumab with docetaxel, in the context of the uncertainty around the long-term benefit (see section 4.3). It noted the company's approach, which used the results of the 12-month analysis and used a generalised gamma curve for extrapolation. It heard from the company that this reflects the decline in mortality rate, which is seen with this novel agent. The committee was mindful of its previous conclusion that nivolumab does offer a gain in survival compared with docetaxel, but not to the extent that is suggested by the results of the company's extrapolation of the data (13.7 months difference for nivolumab over docetaxel). The committee considered that the size of this benefit, which was more than double that of the total overall survival for docetaxel, was unsupported by the clinical evidence. The Committee also understood that the model predicted that mortality risk would decrease over time to a point where people in the model would have a lower risk of death than people of the same age from the general population. The committee understood that the company had applied a constraint in the model to prevent this from happening, however it considered that the need for this constraint suggested that the gamma curve was not a good basis for extrapolating overall survival.The committee therefore went on to discuss the results of the ERG's model, which used the data from the 18-month analysis and an exponential curve for extrapolation, which assumed a constant hazard of

death regardless of length of time on treatment. The committee considered that the ERG's model, which resulted in a gain in mean overall survival of 8.8 months for nivolumab compared with docetaxel was plausible and in line with the clinical expert's opinion on the longer-term mortality benefit of nivolumab. In conclusion, the committee was persuaded that the ERG's approach was more appropriate for extrapolating overall survival.

4.8 The committee discussed the method for modelling overall survival for comparing nivolumab with nintedanib plus docetaxel. The Committee agreed that the proportional hazards assumption was not met. It considered that the same issues regarding the extrapolation of nivolumab affected this comparison as had affected the comparison with docetaxel (see section 4.7). The committee did not feel that this large gain was supported by the trial evidence. It noted that the estimated benefit from the ERG's exploratory analysis, in which the digitised trial data for nintedanib plus docetaxel was extrapolated using an exponential curve, was a mean overall survival gain of 4.1 months for nivolumab. The committee concluded that this was a more clinically plausible estimate of the gain in overall survival for nivolumab when compared with nintedanib plus docetaxel.

4.9 The committee then discussed the method for modelling progression-free survival for comparing nivolumab with docetaxel. It noted that the company used time-to-treatment-discontinuation data from the 12-month results of CheckMate-057 for modelling progression-free survival. It raised concerns about this approach, because it considered that time-to-treatment-discontinuation data should only be used for estimating the costs and adverse events associated with nivolumab, and that progression-free survival data from the trial should have been used for modelling health-state occupancy because it reflects a change in the patients' underlying disease and therefore quality of life. The committee

considered that because progression-free survival data were available from the 18-month data, these would be the most appropriate data to use for modelling progression-free survival. On the method of extrapolation, the committee considered that the same arguments held for extrapolating progression-free survival as for extrapolating overall survival. This was the case for comparing nivolumab with both docetaxel and nintedanib plus docetaxel. The committee therefore concluded that for modelling progression-free survival, data from the 18-month analysis from CheckMate-057 and from LUME-Lung 1 trials, followed by exponential extrapolation, was most plausible for comparing nivolumab with docetaxel and with nintedanib plus docetaxel.

4.10 The committee considered the calculation of costs in the model. It noted that the company calculated the administration costs associated with treatments at the middle of each cycle. The ERG however suggested that these costs should be calculated at the beginning of a cycle, as with the costs of treatment, because that is a clinically more plausible approach. It noted the 2 corrections: the correction applied to the cost per dose of nivolumab, which resulted in a decrease in the average cost per full dose; and the correction in the calculation of administration costs. The committee was aware that these were errors in the model and concluded that these should be corrected.

4.11 The committee discussed the appropriateness of the utility vales used in the company's model. It noted that EQ-5D data were collected in the CheckMate-057 clinical trial and these results were used to calculate the utility values based on the UK value set. The committee noted the ERG's view on the utility values and its comment that in the study, completion rates for filling out EQ-5D questionnaires declined over time. The ERG highlighted that this might have resulted in selection bias and could have influenced the utility values. In its exploratory analyses, the ERG used data from a study published by van den Hout et al. (2016), and calculated

different utility values for both the progression-free and progressed-disease health states. The committee considered that the difference between the utility values used in the progression-free health state (0.739 in the company's model compared with 0.713 used by the ERG) could have been a result of selection bias because of the decline in completing the EQ-5D questionnaires, however it concluded that this difference was not substantial. It noted however, that the difference in the utility values used for the progressed-disease health state were substantially different (0.688 by the company compared with 0.476 by the ERG), because the company did not apply disutility associated with terminal care to the utility value used in the progressed-disease health state. The committee considered that the decline in completing the EQ-5D questionnaire during CheckMate-057 might have resulted in selection bias and influenced the utility values. So, it considered the lower utility values to be more plausible and concluded that a value of 0.713 should be used in the model for the progression-free health state and a utility value of 0.476 for the progressed-disease health state.

4.12 The committee considered the most plausible incremental cost-effectiveness ratio (ICER) for nivolumab compared with docetaxel. It was mindful of its previous conclusions about modelling overall survival, progression-free survival, corrections to the model and the most appropriate utility values, and it recognised that these were all incorporated in the ERG's exploratory analysis which resulted in an ICER of £91,100 per quality-adjusted life year (QALY) gained compared with docetaxel (incremental costs £29,407; incremental QALYs 0.32; including the economic dose cap patient access scheme [PAS]) and that this ICER was above the range of ICERs normally considered a cost‑effective use of NHS resources (£20,000–£30,000 per QALY gained)

4.13 For the comparison of nivolumab with nintedanib plus docetaxel, the committee considered that the analysis that incorporated all its preferred

assumptions, and resulted in an ICER of £93,400 per QALY gained (incremental costs £11,180; incremental QALYs 0.12; including the economic dose cap PAS) was the ERG's exploratory analysis. The committee also noted that there is a confidential simple discount PAS available for nintedanib (the details of which cannot be shown here) and that applying this PAS to the model increased this ICER further. The committee therefore concluded that the most plausible ICER is most likely to be higher than could be considered a cost-effective use of NHS resources.

4.14 The committee noted that the company did not present cost-effectiveness results for comparing nivolumab with BSC and neither did the ERG in its exploratory analyses. The committee considered that there is a patient population, which would not be able to take docetaxel and for whom best supportive care would be the only treatment option. It concluded that the cost-effectiveness analyses results for nivolumab compared with BSC should be calculated. No conclusion on the most plausible ICER for nivolumab compared with BSC was possible with the available analyses (see section 4.4).

4.15 The committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy. It was aware that in line with the transitional arrangement for the Cancer Drugs Fund (CDF) the criterion for small patient population has been taken out. For this advice to be applied, all the following criteria must be met.

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.

In addition, when taking these criteria into account, the committee must be persuaded that the estimates of the extension to life are sufficiently robust and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.16 The committee noted the evidence presented by the company, which showed that people with non-squamous NSCLC have a life expectancy of less than 24 months. The committee then discussed the 3 months' extension-to-life criterion. It noted the results of the cost-effectiveness models and also noted that applying the ERG's preferred assumptions to the model decreased the mean overall-survival benefit of nivolumab when compared with docetaxel or with nintedanib plus docetaxel. The results, however, still showed: an extension-to-life benefit of more than 3 months; a mean of 8.8 months when nivolumab was compared with docetaxel; and a mean of 4.1 months when nivolumab was compared with nintedanib plus docetaxel. The committee therefore concluded that nivolumab met the end-of-life criteria objectively and robustly and that it can be considered a life-extending, end-of-life treatment.

4.17 The committee heard from the company, clinical expert and patient experts that they consider nivolumab to be an innovative treatment and a step-change in managing non-squamous NSCLC due to its novel mechanism of action, which is associated with fewer toxicities than the currently available treatment options. It also noted that, before the marketing authorisation was granted, nivolumab was available for people in the NHS through the Early Access to Medicines Scheme, granted by the UK Medicines and Healthcare products Regulatory Agency. I t concluded that nivolumab is innovative but there were no additional benefits in health-related quality of life that had not been already captured in the QALY calculations.

4.18 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular

the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

4.19 The committee considered the most plausible ICERs for nivolumab compared with docetaxel, nintedanib plus docetaxel, and BSC. It concluded that the ICERs for the first 2 comparisons were much higher than could be considered a cost-effective use of NHS resources. It also considered that because the cost-effectiveness evidence for BSC was not presented, it was unable to make a positive recommendation for nivolumab compared with BSC. In conclusion, it did not recommend nivolumab as a cost-effective use of NHS resources for people with locally advanced or metastatic non-squamous NSCLC after chemotherapy.

Summary of appraisal committee's key conclusions

TAXXX	**Appraisal title: Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer**	**Section**
Key conclusion		
Nivolumab is not recommended for treating locally advanced or metastatic non-squamous non-small-cell lung cancer in adults whose disease has progressed after chemotherapy. • The committee concluded that nivolumab is a clinically-effective treatment option for previously treated non-squamous NSCLC compared with docetaxel, nintedanib plus docetaxel, and best		1.1, 4.19 4.3, 4.4

supportive care (BSC). • The committee considered that nivolumab was innovative and met the criteria to be considered a life-extending, end-of-life treatment. • The most plausible incremental cost-effectiveness ratio (ICER) for nivolumab compared with docetaxel was £91,100 per quality-adjusted life year (QALY) gained. • The most plausible ICER for nivolumab compared with nintedanib plus docetaxel was £93,400 per QALY gained. • Cost-effectiveness evidence compared with BSC was not presented, therefore the committee it was unable to make a positive recommendation for nivolumab compared with BSC. In conclusion the committee did not recommend nivolumab as a cost-effective use of NHS resources for people with locally advanced or metastatic non-squamous non-small-cell lung cancer after chemotherapy.	4.15, 4.16 4.12 4.13 4.14 4.19
Current practice	

Clinical need of patients, including the availability of alternative treatments	People with non-squamous NSCLC have limited treatment options and there is a need for effective treatments, which are not associated with high toxicity. The committee understood that in disease that is not genetic-mutation positive, nivolumab would be a second-line treatment option and that in genetic-mutation-positive disease (either EGFR or ALK positive) nivolumab would be a third-line treatment option. It confirmed with the clinical expert that in both the second- and third-line treatment setting, the comparators would be docetaxel, nintedanib plus docetaxel for people with adenocarcinoma, and best supportive care (BSC) when docetaxel was not a suitable option.	4.1 4.2
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?	The committee heard from the company, clinical expert and patient experts that they consider nivolumab to be an innovative treatment and a step-change in managing non-squamous NSCLC due to its novel mechanism of action, which is associated with fewer toxicities than the currently available treatment options; docetaxel and nintedanib plus docetaxel.	4.17

What is the position of the treatment in the pathway of care for the condition?	The marketing authorisation for nivolumab for non-squamous NSCLC specifies that it is used after chemotherapy. The committee understood that in non-squamous NSCLC that is not genetic-mutation positive, nivolumab would be a second-line treatment option and in genetic-mutation-positive disease (either EGFR or ALK positive) nivolumab would be a third-line treatment option. It also noted that in both the second- and third-line treatment setting, the comparators would be the same; nintedanib plus docetaxel, docetaxel monotherapy, and BSC.	2.1, 4.2
Adverse reactions	The most common adverse reactions with nivolumab in clinical trials were tiredness, decreased appetite and nausea (occurring in more than 10% of people). The summary of product characteristics notes that nivolumab is most commonly associated with immune-related adverse reactions, including pneumonitis, colitis, hepatitis, nephritis and kidney dysfunction, endocrinopathies and rash.	2.2
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The key clinical-effectiveness evidence for nivolumab compared with docetaxel came from the CheckMate-057 clinical trial. The committee noted that data from a 12-month	4.3, 4.4

	interim analysis and an 18-month analysis were available. For comparing nivolumab with nintedanib plus docetaxel, and best supportive care, the company presented the results of an indirect treatment comparison.	
Relevance to general clinical practice in the NHS	Not an issue in this appraisal.	–
Uncertainties generated by the evidence	Neither the company, nor the ERG considered the results of the indirect comparisons a reliable estimate for decision-making on the comparative clinical effectiveness of nivolumab compared with nintedanib plus docetaxel, and best supportive care.	4.4

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The committee noted that the marketing authorisation for nivolumab does not specify PD-L1 mutation expression, nor was it required by the scope for the appraisal, however the, clinical-effectiveness data presented by the company suggested that nivolumab was more effective for those subgroups in which the PD-L1 expression level was above 1%, 5% and 10%; compared with those subgroups in which the PD-L1 expression level was below these thresholds. It also noted that in the latter 3 subgroups, both docetaxel and nivolumab offer similar survival gains. The committee concluded that it could be plausible that nivolumab might have a different level of clinical effectiveness according to PD L1 expression.	4.5

Estimate of the size of the clinical effectiveness including strength of supporting evidence	Nivolumab was associated with statistically significant improvements compared with docetaxel in overall survival. For the comparison with nintedanib plus docetaxel and BSC, neither the company nor the ERG considered the indirect comparison a reliable estimate for decision-making. On the basis of the clinical and patient expert comments, the committee was persuaded that nivolumab would offer some quality-of-life benefit over nintedanib because it avoids the toxicity associated with docetaxel. It further concluded that it is reasonable to expect that nivolumab would offer at least the same survival gain over BSC as docetaxel, and that the quality-of-life gain may be higher due to the difficulties in tolerating docetaxel with the combination therapy.	4.3, 4.4
Evidence for cost effectiveness		
Availability and nature of evidence	The company presented an economic model comparing nivolumab with docetaxel and nintedanib plus docetaxel. The committee accepted the structure of the economic model. Cost-effectiveness evidence for nivolumab compared with BSC was not presented.	4.6, 4.14

Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee considered the following key areas of uncertainty: • The methods used for extrapolating overall survival (for both the comparison between nivolumab with docetaxel and nintedanib plus docetaxel) • The methods used for extrapolating progression-free survival (for both the comparison between nivolumab with docetaxel and nintedanib plus docetaxel) • Utility values used in the model for the progression-free health state and progressed-disease health state, on both arms of the model. • The committee also noted that cost-effectiveness results for comparing nivolumab with BSC were not presented, and concluded that this analysis should be done.	4.7, 4.8, 4.9, 4.11, 4.14

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 considered that the decline in completing the EQ-5D questionnaire during CheckMate-057might have resulted in selection bias and influenced the utility values. It concluded that the utility values calculated by the ERG were more plausible and that a value of 0.713 should be used in the model for the progression-free health state and a value of 0.476 for the progressed-disease health state. The committee concluded that nivolumab is innovative but there were no additional benefits in health-related quality of life that had not been already captured in the QALY calculations.	4.11 4.17
Are there specific groups of people for whom the technology is particularly cost effective?	None.	–
What are the key drivers of cost effectiveness?	The key drivers of cost-effectiveness were the methods used for extrapolating overall survival and the acquisition cost of nivolumab.	4.7, 4.8, 2.4,

Most likely cost-effectiveness estimate (given as an ICER)	The most plausible ICER for nivolumab compared with docetaxel was £91,100 per QALY gained. The most plausible ICER for nivolumab compared with nintedanib plus docetaxel was £93,400 per QALY gained. Cost-effectiveness evidence compared with BSC was not presented, therefore the committee was unable to make a positive recommendation for nivolumab compared with BSC. The committee considered that nivolumab met the criteria to be considered a life-extending, end-of-life treatment. In conclusion, the committee did not recommend nivolumab as a cost-effective use of NHS resources for people with locally advanced or metastatic non-squamous NSCLC after chemotherapy.	4.12, 4.13, 4.14, 4.16, 4.19
Additional factors taken into account		
Patient access schemes (PPRS)	None	4.18

End-of-life considerations	The committee considered that people with non-squamous NSCLC have a life expectancy of less than 24 months. It also concluded that the results of the cost-effectiveness model showed an extension-to-life benefit for nivolumab compared with docetaxel or nintedanib plus docetaxel of more than 3 months. Therefore the committee concluded that nivolumab met the criteria to be considered a life-extending, end-of-life treatment.	4.15, 4.16
Equalities considerations and social value judgements	No equality issues were identified.	–

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 Andrew Stevens
Chair, appraisal committee
May 2016

6 Appraisal committee members, guideline representatives and NICE project team

Appraisal committee members

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

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.

Boglarka Mikudina
Technical Lead

Joanne Holden
Technical Adviser

Stephanie Yates
Project Manager