

**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 4 November 2016**

Second appraisal committee meeting: **to be confirmed**

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 after chemotherapy in adults with a PD-L1 expression of less than 10%.

1.2 The Appraisal committee is minded not to recommend nivolumab as an option for treating locally advanced or metastatic non-squamous non-small-cell lung cancer after chemotherapy in adults with a PD-L1 expression of at least 10%. The committee invites the company to submit a proposal for inclusion in the Cancer Drugs Fund. This proposal should:

- detail any commercial access arrangements
- demonstrate a plausible potential for cost effectiveness
- detail how the proposed data collection will address the key clinical uncertainties described in section 4
- state the likelihood that additional research will reduce uncertainty enough to support positive guidance in the future
- state the proposed data collection approach and current status (for example, an on-going randomised controlled trial, an existing registry or a new data collection proposal)
- state the timeframe for availability of the results
- if appropriate data collection is on-going, summarise the study protocol
- if appropriate data collection is not on-going, and therefore data collection would be started to address the key areas of uncertainty, summarise the proposed data collection protocol specifying:
 - methodology
 - study governance details (information governance, patient consent, ethical approval)
 - analysis plans
 - data access and accountability for disseminating results
 - accountability for monitoring and validation

- any funding arrangements.

1.3 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

Description of the technology	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.
Marketing authorisation	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).
Adverse reactions	The most common adverse reactions with nivolumab are 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.
Recommended dose and schedule	Nivolumab is given intravenously, at a dose of 3 mg/kg body weight every 2 weeks.
Price	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 (assuming 12.6 doses on average, which was the average number of doses in the CheckMate-057 clinical trial). Costs may vary in different settings because of negotiated procurement discounts. The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of nivolumab 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

- 3.1 The appraisal committee ([section 7](#)) 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 is in the company's

evidence submission (pages 41–135) and the ERG report (pages 24–62), and is summarised in the slides presented at the appraisal committee meetings. The cost-effectiveness evidence is in the company's evidence submission (pages 136–242), the appendices to the company's evidence submission and the ERG report (pages 63–121), and is summarised in the slides presented at the appraisal committee meetings.

4 Committee discussion

4.1 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.

Nature of the condition

4.2 The committee noted that non-squamous NSCLC is often diagnosed late in life and causes debilitating and distressing symptoms. The committee heard from clinical experts that people with this condition have limited treatment options, which are all 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. The committee concluded that, given the high toxicity levels of current treatments, people would welcome additional treatment options for non-squamous NSCLC.

Clinical management of the condition

4.3 The committee discussed the management of non-squamous NSCLC in clinical practice. It understood from a clinical expert that platinum therapy is given as an initial 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 people 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 would be used after chemotherapy. Therefore 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 heard from the clinical expert that in both the second- and third-line treatment setting, the comparators would be docetaxel alone, 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 it considered this to be reasonable because these targeted agents would be given before nivolumab and therefore 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

- 4.4 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.

Clinical trial data

- 4.5 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 end point (overall survival) was met at the interim analysis in March 2015 (referred to as the 12-month analysis). The committee considered that the statistically significant median overall-survival gain of 2.8 months for nivolumab compared with docetaxel, as reported in the 12-month 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-month analysis (July 2015), which also showed a statistically significant overall-survival benefit for nivolumab compared with docetaxel. After consultation on the appraisal consultation document, the company submitted the results of the 24-month analysis, which were in line with the previous results. The committee considered that the results of the 3 data cuts were very similar and all suggested a statistically significant minimum median overall-survival gain of 2.7 months for nivolumab over docetaxel. It concluded that all the data could be considered for decision-making, and that nivolumab is clinically effective and offers a gain in survival compared with docetaxel.
- 4.6 The committee heard from the company that the mortality rate for nivolumab declined towards the end of the available trial data, suggesting a decreasing hazard of death with nivolumab as time on treatment increases and beyond the end of treatment. It heard from the company that this long-term survival benefit with nivolumab was 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 clinical practice and in their opinion is likely to be a result of the mechanism of action of nivolumab. The committee also considered the company's comments that a decreasing hazard of death with immuno-oncological treatments for other diseases supports the notion that a decreasing hazard of death is possible with nivolumab. In contrast, the committee heard from the ERG that data from the pivotal trial (CheckMate-057) did not support a decreasing hazard of death, and at around 12 months the data settled to a phase of constant hazard (which implies a long-term constant mortality risk with nivolumab). It also heard from the ERG that data censoring in Checkmate-003 obscured long-term survival in that study. The committee discussed the cumulative hazard plot from CheckMate-003 and a cumulative hazard plot of overall survival from a pooled analysis of ipilimumab (another immuno-oncological technology) for melanoma, which had been provided by the company. However, it did not consider that this evidence supported a constantly decreasing hazard of death with nivolumab. It also noted that a decreasing hazard of death suggests that beyond a certain time point there is almost no mortality risk at all, whether disease- or age-related. The committee reasoned that even if the risk of death caused by the disease decreased over time, the risk of death caused by aging could not decrease over time and could not become zero. It therefore did not consider the company's evidence to be sufficiently robust to take precedence over the analysis of the CheckMate-057 data from the ERG showing a constant mortality risk (that is, the proportion of deaths is expected to remain the same over time, even though the population itself and the absolute number of deaths decreases).

Best supportive care

- 4.7 The committee was aware of the evidence presented by the company for comparing nivolumab with nintedanib plus docetaxel and BSC. The

committee heard from the clinical expert that the rate of adverse reactions with nintedanib plus docetaxel is high and that the benefit seen in clinical 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 views of the company and the ERG that this was not a reliable estimate of comparative effectiveness. On the basis of comments from the clinical and patient experts, the committee was persuaded that nivolumab would offer some quality-of-life benefit over nintedanib plus docetaxel because it avoids the toxicity associated with docetaxel. It 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 greater because of the difficulties in tolerating docetaxel with the combination therapy.

PD-L1 expression

- 4.8 The committee noted that the marketing authorisation for nivolumab does not specify PD-L1 expression, nor was it required by the scope for the appraisal. However, clinical-effectiveness data for PD-L1 subgroups were presented by the company (that is, PD-L1 expression of 1% or more, 5% or more, and 10% or more). It noted that in people whose PD-L1 expression level was below these thresholds, nivolumab and docetaxel offered similar overall-survival benefit. However, in people whose PD-L1 expression level was above these thresholds, nivolumab offered greater overall-survival benefit than docetaxel. This suggested that the higher the level of PD-L1 expression the more effective nivolumab becomes. The committee noted that the benefit was particularly great in people with a

PD-L1 expression of 10% or above, while also noting that this was a small subgroup of patients. The committee noted the company's comment 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. It noted consultation comments from commentators that nivolumab seems to be more effective in subgroups of people with higher levels of PD-L1 expression and therefore overall-survival data should be considered separately for these subgroups. However, the company had not presented any further evidence of the clinical effects of nivolumab in different subgroups of people according to their level of PD-L1 expression. The committee concluded that it is plausible that nivolumab has a different level of clinical effectiveness according to PD-L1 expression. The Committee agreed that data collection to demonstrate the clinical effectiveness of nivolumab in people with at least a 10% PD-L1 expression would resolve some of this uncertainty.

Cost effectiveness

- 4.9 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. The committee also considered the new cost-effectiveness evidence, presented by the company after consultation on the appraisal consultation document, and discussed some of the parameters and assumptions within the model.

Modelling overall survival

- 4.10 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 4.6). It noted the company's original approach, which used the results of the 12-month analysis and a generalised gamma curve for extrapolation. The committee also noted the company's revised approach submitted during consultation, which used the 24-month data and a log-normal curve for extrapolation. It heard from the company that both the generalised gamma and the log-normal approaches reflect a decrease in mortality rate, which the company considered to be evident from the single-arm CheckMate-003 study (see section 4.6). The committee noted its previous conclusion that it did not agree with this interpretation. It also understood that, if extrapolated far enough into the future, both the generalised gamma and the log-normal model would reach a point at which the mortality risk of people who have had nivolumab would be lower than for people of the same age from the general population. The committee accepted that in the revised log-normal model, this point would occur further into the future (and beyond the end of the time horizon for the modelled population) than with the original generalised gamma model. However, it still considered that this concept was not appropriate, nor evidence based. The committee therefore discussed the results of the ERG's model, which used data from the 18-month analysis and an exponential curve for extrapolation. It noted that the 12-month, 18-month and 24-month data were very similar, and it understood that the ERG's approach assumed a constant hazard of death for both the nivolumab and docetaxel groups for the whole of the extrapolated period, which was in line with the clinical evidence (see section 4.6). The committee considered that the outcome of the ERG's model (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. The

committee concluded that the ERG's exponential approach was more appropriate for extrapolating overall survival.

- 4.11 The committee discussed the method for modelling overall survival for comparing nivolumab with nintedanib plus docetaxel. It noted the company's approach of applying hazard ratios to the docetaxel arm of the model, which were calculated based on the comparison of the Kaplan–Meier data from the LUME-Lung 1 trial. The committee heard from the ERG that this approach assumed that the proportional hazards assumption holds (that is, the relative risk of an event is fixed irrespective of time), which was not the case in LUME-Lung 1, as was shown in NICE's technology appraisal guidance on [nintedanib plus docetaxel](#). It also recognised that it is not appropriate to use hazard ratios with a log-normal model. The committee discussed the ERG's approach for estimating overall survival for nivolumab compared with nintedanib plus docetaxel. It heard that this analysis was based on an unadjusted indirect comparison and, as such, had limitations. But it concluded that because this analysis did not assume that the proportional hazards assumption holds, it was more plausible. The committee also considered that this comparison was affected by the same issues regarding the extrapolation of overall survival with nivolumab as had affected the comparison with docetaxel (see section 4.10). It therefore concluded that an exponential model is an appropriate method for extrapolating overall survival for comparing nivolumab and nintedanib plus docetaxel, and that it should be used for calculating the relative cost effectiveness of nivolumab compared with nintedanib plus docetaxel.

Modelling progression-free survival

- 4.12 The committee discussed the method for modelling progression-free survival when 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. The

committee 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. It considered 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 also considered that because continuing treatment after progression is usually determined by a discussion between the clinician and the patient, rather than by an objective criterion, time to treatment discontinuation cannot be considered as a reliable substitute for progression-free survival. The committee considered that because progression-free survival data were available from the more mature data sets (both 18-month and 24-month data), these would be the most appropriate to use for modelling progression-free survival. For the method of extrapolation, the committee considered that the same arguments held for extrapolating progression-free survival as for extrapolating overall survival (see section 4.10). This was the case for comparing nivolumab with both docetaxel alone and with nintedanib plus docetaxel. The committee therefore concluded that for modelling progression-free survival, data from the 24-month analysis from CheckMate-057 and the more mature data from the LUME-Lung 1 trials, followed by exponential extrapolation, were the most appropriate for comparing nivolumab with docetaxel alone and with nintedanib plus docetaxel.

Cost calculations

- 4.13 The committee noted that the company calculated the administration costs associated with treatments at the middle of each cycle in the model. 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. The committee noted 2 corrections; a correction applied to the cost per dose of nivolumab, which resulted in a

decrease in the average cost per full dose, and a correction in the calculation of administration costs. The committee concluded that these were errors in the model and should be corrected.

Dose-intensity reductions

- 4.14 The committee examined the dosing-intensity reduction in the company's economic model. It understood that the company had used dose-intensity reductions for both nivolumab and docetaxel, based upon the dose levels recorded in CheckMate-057. The committee was aware that dosing in trials may be subject to bias because patients under trial conditions are more likely to adhere to the dosing levels. It was aware that in the ERG's analyses, the dosing intensity was revised to levels expressed in the summary of product characteristics. The committee commented that any change in dose intensity should be made to both the intervention and the comparator. It noted that no dosing-intensity adjustment had been made to nintedanib but it heard that nintedanib would be less likely to have a dosing-intensity reduction, because it is an oral therapy. Taking this into account, the committee concluded that it was reasonable to adjust the dosing intensity for both the intervention and the comparator, and it accepted the company's dosing-intensity reductions.

Utility values

- 4.15 The committee noted that EQ-5D data were collected in CheckMate-057 and these results were used in the company's model to calculate the utility values. 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. (2006), 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 for the progression-free health state (0.739 in the company's model compared with 0.713 used by the ERG) could have resulted from selection bias because of the decline in completing the EQ-5D questionnaires, but it concluded that this difference was not substantial. The committee noted however, that the difference in the utility values for the progressed-disease health state were substantially different (0.688 in the company's model compared with 0.476 used 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 questionnaires during CheckMate-057 might have resulted in selection bias and influenced the utility values. It considered the company's revised utility value (0.657) for the progressed-disease health state, presented during consultation on the appraisal consultation document. It understood that this was based on the EQ-5D results from CheckMate-057 and incorporated a disutility associated with terminal care. The committee also considered the ERG's revised utility value (0.480), which accounted for the 25% of patients who had treatment after progression in CheckMate-057, but was still based on the results of the van den Hout et al. study. It noted the company's concern that the population in the van den Hout study was less fit than the population in CheckMate-057 and so the 2 trials should not be considered equal. The committee agreed that this factor might cause the utility value to be lower than might be the case for the population under consideration. However, it was equally concerned that the company's revised utility value (0.657) was higher than values previously accepted for this health state in NSCLC. The committee considered that the company's utility value for the progressed-disease health state was likely to be an overestimation caused by selection bias in CheckMate-057. However, the ERG's utility value might be an underestimation of the true value. Therefore, it concluded that a utility

value between 0.657 and 0.480 should be used in the model for the progressed-disease health state, and a utility value of 0.713 should be used for the progression-free health state.

Duration and cost of treatment with nivolumab

- 4.16 The committee noted that the company included a 2 year clinical stopping rule for people having nivolumab in its economic modelling, but it was aware that in the pivotal clinical trial (CheckMate-037) no stopping rule was applied. The committee heard evidence from the company that in a dose-ranging study of nivolumab in NSCLC (Checkmate-003) a protocol-specified stopping rule was applied at 96 weeks (1.8 years). It heard that 6 out of 7 patients who had a response to treatment (complete or partial) maintained that response beyond 96 weeks. The committee also noted that the company had an ongoing study (Checkmate-153) investigating a 1-year stopping rule and that initial results are due to be published in 2017. The committee understood that the application of a clinical stopping rule would reduce the costs associated with nivolumab and could therefore improve its cost effectiveness if the benefit was maintained beyond 2 years. The committee noted that a 2-year stopping rule was not included in the summary of product characteristics. It reasoned that it was unlikely that clinicians would adhere to a stopping rule that is not specified in the summary of product characteristics, especially if the patient is still benefitting from the treatment. The committee concluded that it was uncertain of the application of a stopping rule in clinical practice and the assumption should not be applied to the economic modelling.

Most plausible incremental cost-effectiveness ratios

- 4.17 The committee considered the cost effectiveness of nivolumab compared with docetaxel for treating locally advanced or metastatic non-squamous non-small-cell lung cancer that has progressed after chemotherapy in adults. It noted that in the company's base case the incremental cost-

effectiveness ratio (ICER) was below £50,000 per quality-adjusted life year (QALY) gained when the nivolumab patient access scheme was used (exact ICERs are commercial in confidence so cannot be reported here). The committee noted that when the modelling assumptions were altered, in most cases the ICER was above £50,000 per QALY gained. When the committee's preferred modelling assumptions (see sections 4.10 to 4.15) were used the ICER increased to over £80,000 per QALY gained. It further noted that when the 2-year clinical stopping rule was used (see section 4.16) the ICER remained above £50,000 per QALY gained. The committee concluded that the most plausible ICER was above the range normally considered a cost-effective use of NHS resources, even taking into account additional weights applied to QALY benefits for a life-extending treatment at the end of life (see section 4.20).

4.18 When comparing nivolumab with nintedanib plus docetaxel for treating locally advanced or metastatic non-squamous non-small-cell lung cancer that has progressed after chemotherapy in adults, the committee considered that the ERG's revised exploratory analysis incorporated all its preferred assumptions (see sections 4.10 to 4.15). The committee noted that including the patient access schemes for nivolumab and nintedanib resulted in an ICER above £150,000 per QALY gained (the exact ICER is commercial in confidence so cannot be reported here). It also noted that even if a 2-year clinical stopping rule was applied, the ICER would be above £70,000 per QALY gained. The committee therefore concluded that the most plausible ICER was above the range normally considered a cost-effective use of NHS resources, even taking into account additional weights applied to QALY benefits for a life-extending treatment at the end of life (see section 4.20).

4.19 The committee noted that neither the company nor the ERG presented cost-effectiveness results comparing nivolumab with BSC. The committee

considered that there is a patient population who cannot have docetaxel (because it is contraindicated or not tolerated) and for whom BSC would be the only treatment option. It concluded that it would have preferred to have a cost-effectiveness analysis of nivolumab compared with BSC. No conclusion on the most plausible ICER for nivolumab compared with BSC was possible with the available analyses (see section 4.7).

End-of-life considerations

- 4.20 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 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 discussed the 3 months' extension-to-life criterion. It noted the results of the cost-effectiveness models and that applying the ERG's preferred assumptions to the model decreased the mean overall-survival benefit of nivolumab, compared with docetaxel alone or with nintedanib plus docetaxel. However, the results 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.

Innovation

- 4.21 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 because of its novel mechanism of action, which is associated with fewer adverse reactions than the currently available treatment options. It also noted that, before

the marketing authorisation was granted, nivolumab was available in the NHS through the early access to medicines scheme. It 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.

Pharmaceutical Price Regulation Scheme (PPRS) 2014

- 4.22 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.

Cancer Drugs Fund

- 4.23 The committee considered whether nivolumab for locally advanced or metastatic non-squamous NSCLC after chemotherapy could be considered for inclusion in the Cancer Drugs Fund. Under the new arrangements, drugs that appear promising, but for which the evidence is not strong enough for routine use, may be given a conditional recommendation by NICE and made available to NHS patients through the Cancer Drugs Fund. Such a drug will remain available within the Cancer Drugs Fund, normally for up to 2 years, while more data are collected. The committee was aware that in considering this, the following criteria must be met:

- The ICERs have the plausible potential for satisfying the criteria for routine use
- It is possible that the clinical uncertainty can be addressed through collection of outcome data from patients treated in the NHS
- It is possible that the data will be able to inform a subsequent update of the guidance (normally within 24 months).

4.24 The committee agreed that the ICERs for the full licensed population did not indicate a plausible potential for cost effectiveness (see sections 4.17 and 4.18). However it questioned whether nivolumab has the plausible potential for satisfying the criteria for routine use for a subgroup of people with high PD-L1 expression. It noted its earlier conclusion regarding the clinical effectiveness of nivolumab that those with a PD-L1 expression level of at least 10% seemed to have the greatest potential to benefit from treatment with nivolumab (section 4.8). The committee was also aware that the company's application of a treatment stopping rule had substantially reduced the ICERs. Whilst it remained of the opinion that the stopping rule could not be implemented in NHS clinical practice (see section 4.16) the committee was aware that if nivolumab were to be funded within the Cancer Drugs Fund, after 2 years of treatment the acquisition cost of the drug would transfer to the company (that is, part of the agreed commercial arrangement would require that the company continue to provide nivolumab to people receiving it after the 2 year funding period ends). The committee reasoned that the cost effectiveness of nivolumab for a subgroup of people with at least 10% PD-L1 expression could be more favourable than the estimates presented for the full population. However it acknowledged that as it had not been presented with the cost effectiveness estimates for subgroups of patients according to the level of PD-L1 expression, it could not judge whether this would be the case, and so it considered it unreasonable to recommend nivolumab for this subgroup for inclusion in the Cancer Drugs Fund at this stage of

the appraisal. Instead, the committee signalled that this could be an option if the company were to present estimates of cost effectiveness that would allow it to make this judgement.

4.25 In considering whether the main uncertainties could be addressed through data collection, the committee understood that ongoing trials aim to assess the efficacy of nivolumab according to PD-L1 expression. It was also aware of ongoing research into clinical outcomes for people who stop treatment before 2 years. The committee considered that the ongoing research may help to resolve some of the uncertainties. The committee was further reassured that, as part of the process of considering nivolumab for inclusion within the Cancer Drugs Fund, the Committee would have the opportunity to consider the data collection arrangements, timeframe, and the commercial access arrangements agreed by the company and NHS England, before providing a final recommendation for use within the Cancer Drugs Fund.

4.26 In summary, the committee concluded that nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer was not recommended for the broader licensed indication. It was also minded not to recommend nivolumab for a subgroup of people with a PD-L1 expression of at least 10%, as no cost-effectiveness evidence had been provided stratified by PD-L1 expression. The committee however, invited the company to submit a proposal for inclusion in the Cancer Drugs Fund for a subgroup of people with PD-L1 expression of at least 10%, and to lay out how data collection in the Cancer Drugs Fund will address the main (clinical) uncertainties.

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		
<p>Nivolumab is not recommended for routine use in the NHS because it has not been shown to be cost effective for all people covered by the marketing authorisation for non-squamous non-small-cell lung cancer.</p> <p>The committee is minded not to recommend nivolumab for a subgroup of people with a PD-L1 expression of at least 10% for inclusion in the Cancer Drugs Fund, because no cost effectiveness estimates have been presented. The committee has invited the company to submit a proposal for inclusion in the Cancer Drugs Fund for this subgroup, detailing how data collection may resolve some of the uncertainties.</p>		1.1, 1.2, 4.5, 4.17, 4.18, 4.20, 4.21, 4.23

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 that are not associated with high toxicity.	4.2
	The committee heard from the clinical expert that in both second- and third-line treatment settings, treatment options include docetaxel alone, nintedanib plus docetaxel for people with adenocarcinoma, and best supportive care (BSC) when docetaxel is not a suitable option.	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?	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 because of its novel mechanism of action, which is associated with fewer adverse reactions than the currently available treatment options (docetaxel and nintedanib plus docetaxel).	4.21
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-	Table 1, 4.3

	squamous NSCLC that is not genetic-mutation positive, nivolumab would be a second-line treatment option. In genetic-mutation-positive disease (either EGFR- or ALK-positive) nivolumab would be a third-line treatment option. It also noted that in both second- and third-line treatment settings, the comparators would be the same; docetaxel alone, nintedanib plus docetaxel, and BSC.	
Adverse reactions	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
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	<p>The key clinical-effectiveness evidence for nivolumab compared with docetaxel came from the CheckMate-057 clinical trial. Analysis at 12, 18 and 24 months suggested a statistically significant minimum overall-survival gain of 2.7 months for nivolumab over docetaxel.</p> <p>For comparing nivolumab with nintedanib plus docetaxel, and BSC, the company presented the results of an indirect treatment comparison.</p>	<p>4.5</p> <p>4.7</p>

Relevance to general clinical practice in the NHS	Not an issue in this appraisal.	–
Uncertainties generated by the evidence	Neither the company, nor the evidence review group (ERG), considered the results of the indirect comparisons to be a reliable estimate of the clinical effectiveness of nivolumab compared with nintedanib plus docetaxel, or with BSC.	4.7
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	<p>The clinical-effectiveness data presented suggest that nivolumab is more effective than docetaxel for subgroups in which the PD-L1 expression level is above 1%, 5% and 10%, compared with those subgroups in which the PD-L1 expression level is below these thresholds.</p> <p>The committee concluded that it is plausible that nivolumab has a different level of clinical effectiveness according to PD-L1 expression. The Committee agreed that data collection to demonstrate the clinical effectiveness of nivolumab in people with at least a 10% PD-L1 expression would be valuable</p>	4.8
Estimate of the size of the clinical effectiveness including strength of supporting evidence	Nivolumab was associated with statistically significant improvements in overall survival compared with docetaxel. For the comparison with nintedanib plus docetaxel and BSC, neither the company nor the ERG considered	4.5, 4.7

	<p>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 because of the difficulties in tolerating docetaxel with the combination therapy.</p>	
Evidence for cost effectiveness		
Availability and nature of evidence	<p>The company presented an economic model comparing nivolumab with docetaxel and nivolumab with nintedanib plus docetaxel. The committee accepted the structure of the economic model.</p> <p>Cost-effectiveness evidence for nivolumab compared with BSC was not presented.</p>	<p>4.9</p> <p>4.19</p>
Uncertainties around and plausibility of assumptions and inputs in the economic model	<p>The committee considered the following key areas of uncertainty:</p> <ul style="list-style-type: none"> • the methods used for extrapolating overall survival • the methods used for extrapolating progression-free survival 	<p>4.10, 4.11, 4.12, 4.15, 4.16</p>

	<ul style="list-style-type: none"> • utility values used in the model for the progression-free and progressed-disease health states • application of a 2 year clinical stopping rule. 	
<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The committee considered that selection bias might have influenced the EQ-5D results from CheckMate-057 and the utility values for the progression-free health state presented by the company. It considered that the utility value presented by the ERG (0.713) was more plausible.</p> <p>The committee considered that the company’s estimated utility values for the progressed-disease health state (based on CheckMate-057) may be overestimated due to selection bias, and the ERG utilities may be underestimated due to the source study. It concluded that a utility value between 0.657 (company value) and 0.480 (ERG value) should be used in the model for the progressed-disease health state.</p> <p>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.</p>	<p>4.15, 4.21</p>
<p>Are there specific groups of people for</p>	<p>The committee concluded that no cost-effectiveness evidence had been provided</p>	<p>4.26</p>

whom the technology is particularly cost effective?	stratified by PD L1 expression.	
What are the key drivers of cost effectiveness?	The key drivers of cost-effectiveness were the methods used for extrapolating overall survival, the acquisition cost of nivolumab, and the application of a 2 year stopping rule.	4.10, 4.11, 4.13, 4.16
Most likely cost-effectiveness estimate (given as an ICER)	<ul style="list-style-type: none"> • The most plausible ICER for nivolumab compared with docetaxel was above £80,000 per QALY gained. • The most plausible ICER for nivolumab compared with nintedanib plus docetaxel was above £150,000 per QALY gained. <p>Cost-effectiveness evidence comparing BSC was not presented, therefore the committee was unable to make a positive recommendation for nivolumab compared with BSC.</p>	4.17–4.19
Additional factors taken into account		
Patient access schemes (PPRS)	There are patient access schemes for nintedanib and nivolumab. Both schemes are confidential simple discounts.	2, 4.15

End-of-life considerations	The committee considered that people with non-squamous NSCLC have a life expectancy of less than 24 months. It 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.	4.20
Equalities considerations and social value judgements	No equality issues were identified.	—

5 Proposed date for review of guidance

- 5.1 The proposed review date for the guidance on this technology should be 3 years after publication of the guidance unless the technology is to be included within the Cancer Drugs Fund in which case the review date would be in line with the standard operating procedures for the Cancer Drugs Fund. This will be confirmed upon publication of the final guidance for this appraisal.

Professor Andrew Stevens
 Chair, appraisal committee
 October 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 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 an Associate Director, 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Frances Sutcliffe

Associate Director

Henry Edwards and Boglarka Mikudina

Technical Leads

Joanne Holden

Technical Adviser

Stephanie Yates

Project Manager

ISBN: [to be added at publication]