NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Nivolumab for previously treated non-squamous non-small-cell lung cancer

1. Recommendations

1.1 Nivolumab is recommended for use within the Cancer Drugs Fund as an option for treating locally advanced or metastatic non-squamous non-small-cell lung cancer in adults after chemotherapy, only if:

- their tumours are PD-L1 positive and
- nivolumab is stopped at 2 years of uninterrupted treatment, or earlier in the event of disease progression, and
- the conditions in the managed access agreement are followed.

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

2. The technology

Description of the technology	Nivolumab (Opdivo, Bristol–Myers Squibb) is a monoclonal antibody that targets a receptor on the surface of lymphocytes known as the programmed cell death protein-1 (PD-1) receptor. 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.
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; 'British national formulary' [BNF], accessed online April 2017). This equates to £2,634 per dose, and £5,268 per month, for a person weighing 73 kg. As part of the managed access agreement, the company (Bristol–Myers Squibb) has a commercial access agreement with NHS England. This makes nivolumab available at a reduced cost. The financial terms of the agreement are commercial in confidence.

3. Evidence

3.1 The appraisal committee (section 7) considered comments on the second appraisal consultation document, petitions, new evidence submitted by Bristol–Myers Squibb, a review of this submission by the evidence review group and a report from the NICE Decision Support Unit. After this meeting, production of the final appraisal determination was paused for Bristol–Myers Squibb and NHS England to have commercial discussions. Further new evidence submitted by Bristol–Myers Squibb was reviewed

by the NICE Decision Support Unit and considered by the committee at the fifth meeting. See the committee papers for full details of the evidence.

3.2 Sections 4.1 to 4.27 reflect the committee's discussion of the evidence submitted for the first to fourth appraisal committee meetings. Section 4.28 (Cancer Drugs Fund) onwards reflects the committee's most recent discussion of the new evidence (clinical and cost-effectiveness subgroup analyses by PD-L1 expression) and the commercial access agreement submitted for consideration in the Cancer Drugs Fund, and discussed at the fifth appraisal committee meeting. The committee's overall conclusions are described in sections 4.34 and 4.35.

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 previously treated locally advanced or metastatic 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

4.1 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 noted that this view was supported by stakeholders in comments on the second appraisal consultation document. It also heard from patient experts that chemotherapy is often 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 toxicity levels of current treatments, people would welcome additional treatment options for non-squamous NSCLC.

Clinical management of the condition

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 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 is used after chemotherapy. Therefore, it agreed with the clinical expert and the company that in disease that is not genetic-mutation positive (neither EGFR- nor ALK-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.

Comparators

4.3 The committee 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 noted comments from the company during the first and second consultations that they consider that docetaxel is the only relevant comparator. However the committee heard from clinical experts that around 70% of people with non-squamous NSCLC have adenocarcinoma, for which nintedanib plus docetaxel is a recommended treatment option. It understood that nintedanib plus docetaxel is associated with high levels of toxicity and only those able to tolerate 4 cycles of docetaxel were likely to have nintedanib. Despite this, the committee considered nintedanib plus docetaxel a relevant comparator. It was aware that the company had also not provided comparisons of nivolumab 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 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 results showed a statistically significant median overall survival gain for nivolumab compared with docetaxel. It also considered that this was supported by the results of the 18-month and 24-month analyses, as well as the most recent 36-month analysis, which were in line with the previous results. The committee considered that the results of the 4 data cuts were very similar and all suggested a statistically significant median overall survival gain of at least 2.7 months for nivolumab over docetaxel (the overall survival difference ranged from 2.7 months to 3.4 months). It also considered that this was an important extension-to-life benefit for people with advanced NSCLC who have had chemotherapy. 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 at the first committee meeting, 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 result from nivolumab's mechanism of action. The committee also considered the company's comments that a decreasing hazard of death with immuno-oncological treatments for other diseases supports the view that a decreasing hazard of death is possible with nivolumab. In contrast, the committee heard from the evidence review group (ERG) that data in the company's first submission 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).

PD-L1 expression

4.7 The committee noted that the marketing authorisation for nivolumab does not specify programmed cell death ligand-1 (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. Also, in people with unquantifiable PD-L1 expression, the overall survival benefit with nivolumab was similar to that with docetaxel. However, in people whose PD-L1 expression level was above these thresholds, nivolumab offered greater overall survival benefit than docetaxel. This suggested nivolumab becomes more effective as the level of PD-L1 expression rises. The committee noted that the benefit was particularly great in people with a PD-L1 expression of 10% or above, but was aware 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 comments at the first consultation 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. The committee considered further new clinical evidence

submitted by the company in its final decision making (discussed in section 4.30 to 4.37).

Nivolumab compared with nintedanib plus docetaxel and best supportive care

4.8 The committee considered the original submission evidence presented by the company which compared nivolumab with nintedanib plus docetaxel, and with 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 clinical effectiveness. Based on 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 it would offer better quality of life over nintedanib plus docetaxel because of the difficulties in tolerating docetaxel with the combination therapy.

Cost effectiveness

4.9 The committee discussed the original cost-effectiveness evidence submission presented by the company and its critique by the ERG. It accepted the structure of the economic model developed by the company. The committee noted its recommendation for people with a PD-L1 expression of at least 10% in the second appraisal consultation document, and its invitation to the company to submit a proposal for inclusion in the

Cancer Drugs Fund. The committee was aware that the company did not submit a Cancer Drugs Fund proposal for the PD-L1 subgroup in response to the second appraisal consultation document, but instead continued with an alternative, but new, proposal for the whole population.

4.10 The committee noted that the company's new proposal also included an alternative extrapolation curve, in addition to new evidence and analyses addressing some of the committee's uncertainties in the appraisal. The committee considered the new cost-effectiveness and supporting evidence presented by the company, stakeholder comments on the second appraisal consultation document, and 2 petitions. The committee also considered a report commissioned by NICE from the NICE Decision Support Unit (DSU) who were asked to:

- explore the goodness of fit for all overall survival extrapolation curves (the company's 'intermediary' curve in response to the second appraisal consultation document, the curve preferred by the committee in the second appraisal consultation document, and company's original curves)
- explore rationales for a 2-year stopping rule and uncertainty of the long-term treatment effect
- propose an overall-survival curve fit preferred by the DSU and the reasons for the choice.

The committee was also aware that the company took account of the outcomes from the DSU's report and submitted additional new supporting evidence after the production of the DSU report. It noted that the company's new evidence included a new (3-year) data cut from CheckMate 057 and CheckMate 003.

Modelling overall survival

4.11 The committee discussed the methods 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 the first 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 neither 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, 24-month and 36-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 4.5). 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 original exponential approach was more appropriate for extrapolating overall survival.

4.12 The committee noted that the approaches used by the company and the ERG to extrapolate overall survival had a major effect on the results of the

economic model. It recalled that after the consultation on the second appraisal consultation document and receiving a new proposal from the company, NICE had commissioned the NICE DSU to explore the goodness of fit for all overall survival extrapolation curves, and propose a preferred curve fit. The committee also noted that the DSU agreed with the ERG's and committee's preferred approach to extrapolating overall survival (using both the Kaplan–Meier curve from the trial and an exponential curve for extrapolation; see section 4.10). The committee heard from the company that the new clinical evidence from CheckMate 057 and CheckMate 003 supported using the log-normal curve and inspected the new evidence presented by the company. It heard from the ERG that the company had not reproduced the ERG's approach appropriately when comparing the extrapolation methods. It understood that the DSU considered the extrapolation of overall survival uncertain, especially given the small number of people still alive at the tail of the observed data (the number of people alive at 36 months was 50 for CheckMate 057 and 16 for CheckMate 003). The committee also heard from the DSU that in the first 2 years, the log-normal curve overestimated survival compared with the observed data and that the log-normal curve presented an optimistic view of the survival benefit of nivolumab. After careful consideration, the DSU's choice of curve was the committee-preferred hybrid Kaplan–Meier/exponential approach to extrapolate overall survival. The committee concluded that after considering the new evidence and expert advice, the method used by the ERG and the DSU to extrapolate overall survival was the most appropriate approach.

4.13 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. 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.

Extrapolation of progression-free survival

4.14 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 4.11). This was the case for comparing nivolumab with both docetaxel alone and with nintedanib plus docetaxel. The committee agreed 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.

4.15 The committee was aware that, in response to the second appraisal consultation document, the company presented new evidence using alternative approaches to extrapolate progression-free survival for the whole population (including Weibull and gamma extrapolations). It noted that the alternative approaches to extrapolate progression-free survival did not have a major impact and led to an average decrease in the cost-effectiveness estimates of around £2,500 per quality-adjusted life year (QALY) gained. However, the company did not present any evidence to support this or a reason for using alternative extrapolation approaches, and it did not find any reason to depart from its previously agreed approach. The committee therefore concluded that using the observed data followed by an exponential extrapolation was the most appropriate method to estimate progression-free survival.

Treatment costs

4.16 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

4.17 The committee examined the dose-intensity reduction in the company's economic model. It understood that the company had used dose-intensity reductions for both nivolumab and docetaxel, based on the dose levels recorded in CheckMate 057. The committee was aware that there may be bias in dosing because, under trial conditions, patients are more likely to follow dosing schedules. It was aware that in the ERG's analyses, the dose intensity was revised to levels recommended 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 dose-intensity adjustment had been made to nintedanib, but it heard that nintedanib would be less likely to have a dose-intensity reduction because it is an oral therapy. Taking this into account, the committee concluded that it was reasonable to adjust the dose intensity for both the intervention and the comparator, and it accepted the company's dose-intensity reductions.

Utility values

4.18 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.

4.19 The committee considered that, in its final revised modelling approach, the company changed the utility values and applied the committee's preferred values. Therefore, utility values of 0.713 and 0.569 were used for the progression-free and progressed-disease health states respectively. The committee concluded that these values are more likely to represent the real value of the health-related quality of life associated with the different health states in the model.

Continued treatment effect

4.20 The committee considered the duration of treatment effect after treatment had stopped. It heard from the company that the mechanism of action of nivolumab suggested that its effects on tumours would continue after treatment stopped. The committee considered that it was biologically plausible that the effects of nivolumab might continue after treatment stops, but was concerned that there is a lack of evidence to support this. The committee recalled new supportive 36-month results from the CheckMate 057 trial presented after consultation on the second appraisal consultation document, and noted that the differences between the nivolumab arm and the docetaxel arm were maintained. The committee agree that although it was biologically plausible for treatment effects to continue after stopping treatment, the exact continued effect was uncertain. It concluded that, based on the available clinical evidence it was plausible that after stopping treatment at 2 years, nivolumab's treatment effect could last up to 3 years.

Stopping rule

4.21 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 no stopping rule was applied in the pivotal clinical trial (CheckMate 037). The committee heard 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 the first results are due to be published in 2017. The committee understood that applying a clinical stopping rule would reduce the costs associated with nivolumab and could therefore improve its cost effectiveness, if the benefit continued after 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 follow a stopping rule that is not specified in the summary of product characteristics, especially if the person was still benefitting from the treatment. The committee noted comments on the appraisal consultation documents made by NHS England and other consultees that that a 2-year stopping rule is acceptable to both patients and clinicians and would be implementable. The committee's concerns were eased by assurances from NHS England and concluded that a 2-year stopping rule should be applied in the economic model.

Cost-effectiveness results

4.22 The committee considered the cost effectiveness of nivolumab compared with docetaxel alone incorporating the updated patient access scheme. The committee noted that the company's new base-case cost-effectiveness results in its final revised modelling approach, which included a 2-year data cut from CheckMate 057, ranged from £53,800 to £61,500 per QALY gained, depending on the level of continued treatment effect applied. It examined cost-effectiveness results provided by the company that included the committee's preferred assumptions (see sections 4.9 to 4.21) for:

- extrapolating overall survival – using the exponential curve (see section 4.11)
- extrapolating progression-free survival – using the exponential curve (see section 4.14)
- utility values (see section 4.18)
- applying a 2-year stopping rule (see section 4.21)
- the treatment effect duration – up to 3 years after stopping treatment (see section 4.20).

However, the committee heard from the ERG that the committee's preferred approach for extrapolating overall survival had not been calculated properly. The committee requested corrected cost-effectiveness results for nivolumab compared with docetaxel, including the committee's preferred assumptions and the updated patient access scheme. The committee received updated results from the company that also included 3-year overall survival data. The incremental cost-effectiveness ratio (ICER) submitted (£57,976 per QALY gained) was much less than the £76,137 that the committee provisionally accepted at its fourth meeting. The £57,976 per QALY gained ICER was unverified by the DSU but the committee heard that it was plausible even though there was still considerable uncertainty. The proposed patient access scheme was subsequently replaced with a commercial access agreement at the fifth appraisal committee meeting (discussed in section 4.28 onwards), which reduced the ICER for nivolumab compared with docetaxel to £49,122 per QALY gained.

4.23 The committee was aware that the company had proposed scenario analyses incorporating cost savings for nivolumab in other indications based on the updated proposed patient access scheme for NSCLC. It was also aware that there would be a wider benefit to the NHS because the simple discount agreed in the patient access scheme would apply across all indications. However, it noted that taking this into account was outside its approved methods. The committee was also concerned that there was

no details on how the discounts were calculated and applied. It concluded that it was not appropriate to incorporate these benefits into the economic model, taking into account the most plausible ICER and the uncertainty identified.

4.24 The committee considered the cost-effectiveness estimates of nivolumab compared with nintedanib plus docetaxel for treating locally advanced or metastatic NSCLC that has progressed after chemotherapy in adults. The committee noted that the most plausible cost-effectiveness estimate, which included the committee's preferred assumptions and the confidential patient access schemes for nivolumab and nintedanib, resulted in an ICER above £100,000 per QALY gained (the exact ICER is commercial in confidence so cannot be reported here). The committee therefore did not recommend nivolumab as a cost-effective use of NHS resources for treating locally advanced or metastatic non-squamous NSCLC after chemotherapy in people for whom nintedanib plus docetaxel is an option.

4.25 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 had a cost-effectiveness analysis of nivolumab compared with BSC, however none was provided. Therefore, there was no ICER presented for nivolumab compared with BSC and the committee did not make a recommendation for people who cannot have docetaxel and for whom BSC would be the only treatment option.

End-of-life considerations

4.26 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

locally advanced or metastatic 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 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

4.27 The committee heard from the company, clinical experts, patient experts and consultees 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.

Cancer Drugs Fund

4.28 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. The committee discussed the new arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting the addendum to the NICE process and methods guides. 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 must have the plausible potential for satisfying the criteria for routine use.
- It is possible that the clinical uncertainty can be addressed by collecting outcome data from patients having treatment in the NHS.
- It is possible that the data will be able to inform a subsequent update of the guidance (normally within 24 months).

4.29 At the fourth appraisal committee meeting, the committee agreed that the ICERs for the full non-squamous NSCLC population did not show a plausible potential for cost effectiveness (see sections 4.22 to 4.25**Error! Reference source not found.**). 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 that those people with a PD-L1 expression level of at least 10% seemed to have the greatest potential to benefit from treatment with nivolumab (see section 4.7). The committee reasoned that the cost effectiveness of nivolumab for a subgroup of people with at least a 10% PD-L1 expression could be more favourable than the estimates presented for the full population. However, because 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 inclusion in the Cancer Drugs Fund at this stage of the appraisal. Instead, the committee noted that this could be an option if the company presented estimates of cost effectiveness that allowed it to make this judgement. The company

declined to make a proposal for inclusion into the Cancer Drugs Fund for a subgroup of people with at least 10% PD-L1 expression.

4.30 At the fifth appraisal committee meeting, the company presented new evidence and a commercial access agreement proposal for inclusion into the Cancer Drugs Fund for the full non-squamous NSCLC population. This included the committee's preferred assumptions, overall survival data from the most recent 3-year data cut from CheckMate 057 and a new commercial access agreement (see section 4.22). The committee noted that the company did not present cost-effectiveness results for nivolumab compared with nintedanib plus docetaxel in this updated analysis.

4.31 The committee noted that the DSU suggested the following corrections to the model:

- In the company's model, when the progression-free survival and overall survival curves cross, overall survival was corrected to be as high as progression-free survival. However progression-free survival should be corrected to never be higher than overall survival because the estimate of overall survival is less uncertain than that of progression-free survival.
- After the continued treatment effect period (3-years, see section 4.20), the DSU applied the hazard ratio of the docetaxel arm to the nivolumab arm for progression-free survival.

The committee agreed that these corrections were appropriate and should be applied to the model. As a result of these changes the most plausible ICER for nivolumab compared with docetaxel changed to £49,160 per QALY gained the full non-squamous NSCLC population.

4.32 The committee looked at the clinical evidence presented by the company with the 2-year data cut showing subgroup analyses according to the level of PD-L1 expression, as well as the evidence presented in the European Public Assessment Report from the European Medicines Agency. It

considered that nivolumab showed better effectiveness than docetaxel in the subgroups in which PD-L1 expression was positive, however it also accepted that nivolumab showed similar or worse effectiveness to docetaxel in the subgroups in which PD-L1 expression was negative, and in which PD-L1 expression level was unquantifiable.

4.33 On request, the company presented cost-effectiveness results including subgroup analyses based on PD-L1 expression. This included the committee's preferred assumptions, overall survival data from the most recent 3-year data cut from CheckMate 017 and a new commercial access agreement. The results of the subgroup analyses were considered as commercial in confidence, so the exact ICERs cannot be reported here. The committee heard from the DSU that it had concerns about the plausibility of the subgroup analyses because of the small patient numbers in the subgroups and methods used for extrapolating overall survival and progression-free survival. Having concluded that nivolumab has shown no convincing overall survival benefit versus docetaxel for patients whose tumours were PD-L1 negative or where the PD-L1 level was unquantifiable in the clinical evidence presented to it, the committee considered it reasonable to exclude those patients from the cost-effectiveness considerations. Considering that the most plausible ICER, after the DSU's corrections, for the full non-squamous NSCLC population was £49,160 per QALY gained (see section 4.31), it considered it reasonable to recommend nivolumab for inclusion in the Cancer Drugs Fund for people with tumours that are PD-L1 positive.

4.34 In the absence of any calculations from the company concerning the comparison with nintedanib plus docetaxel, the committee considered the separate calculations for nivolumab (submitted by the company to the fifth meeting) and nintedanib plus docetaxel (considered in the fourth committee meeting) and noted that considerable uncertainty remains for this comparison, both in terms of clinical and cost effectiveness (see also sections **Error! Reference source not found.** and **Error! Reference source not found.**). Despite this, the committee concluded that

nivolumab had plausible potential for being cost effective in the subgroup of patients whose tumours were PD-L1 positive when further long-term data is collected for comparison with nintedanib plus docetaxel.

4.35 The committee finally considered the subgroup of patients with unquantifiable PD-L1 expression and noted that one of the reasons why people can have unquantifiable results can be because of operational issues around PD-L1 testing. The committee understood that this group could include people with PD-L1-positive non-squamous NSCLC whose expression has not been identified because of lack of sample or insufficient test result, but it heard from the Cancer Drugs Fund clinical lead that occurrence of this issue is diminishing. The committee concluded that it would not have to accommodate for this in its recommendations.

Overall conclusions

4.36 The committee recalled its earlier conclusions that the most plausible ICERs for nivolumab compared with docetaxel and nintedanib plus docetaxel were above the range that is normally considered a cost-effective use of NHS resources (see section 4.22). It acknowledged that nivolumab met the criteria to be considered a life-extending end-of-life treatment (see section 4.26), and concluded that the ICERs were not within the range usually 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. It therefore did not recommend nivolumab for treating locally advanced or metastatic non-squamous NSCLC after chemotherapy in routine commissioning.

4.37 The committee took into account the company's further new analysis which included overall survival data from a 3-year data cut from CheckMate 057, a new commercial access agreement and new clinical data. It concluded that based on the clinical evidence it was presented with at the fifth appraisal committee meeting (see section 4.32) and the most plausible ICER after the DSU's corrections for the full non-squamous

NSCLC population (that is £49,160 per QALY gained, see section 4.31) nivolumab had shown plausible potential for cost effectiveness for the subgroup of people with PD-L1 positive tumours. It therefore recommended nivolumab for treating locally advanced or metastatic non-squamous NSCLC in adults after chemotherapy for use within the Cancer Drugs Fund, only if their tumours are PD-L1 positive and the conditions of the managed access agreement are followed.

Summary of appraisal committee's key conclusions

TAXXX	**Appraisal title: Nivolumab for previously treated non-squamous non-small-cell lung cancer**	**Section**
Key conclusion		
Nivolumab is recommended for use within the Cancer Drugs Fund as an option for treating locally advanced or metastatic non-squamous non-small-cell lung cancer in adults after chemotherapy, only if: • their tumours are PD-L1 positive and • nivolumab is stopped at a maximum of 2 years of uninterrupted treatment when there is no documented disease progression, and • the conditions in the managed access agreement are followed.		1.1
The committee took into account the company's further new analysis which included their preferred assumptions, a 3-year data cut from CheckMate 057, a new commercial access agreement and new clinical data. It concluded that based on the clinical evidence and the most plausible ICER after the DSU's corrections for the full non-squamous NSCLC population (that is £49,160 per QALY gained, see section 4.31), nivolumab had shown plausible potential for cost effectiveness for the subgroup of patients whose tumours were PD-L1-positive compared with docetaxel and with nintedanib plus docetaxel. It therefore recommended		4.30 to 4.35, 4.25

nivolumab for treating locally advanced or metastatic non-squamous NSCLC in adults after chemotherapy for use within the Cancer Drugs Fund, only if their tumours are PD-L1 positive and the conditions of the managed access agreement are followed. For nivolumab compared with best supportive care (BSC), the committee was not able to make a recommendation because it has not been presented with cost-effectiveness results for this population.		
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. 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 BSC when docetaxel is not a suitable option.	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?	The committee heard from the company, clinical experts, patient experts and consultees 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).	4.27

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. In genetic-mutation-positive disease (either epidermal growth factor receptor [EGFR]- or anaplastic lymphoma kinase [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.	2 4.2, 4.3
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	The key clinical-effectiveness evidence for nivolumab compared with docetaxel came from the CheckMate 057 clinical trial. Analysis at 12, 18, 24 and 36 months suggested a statistically significant minimum overall survival gain of at least 2.7 months for nivolumab over docetaxel. For comparing nivolumab with nintedanib plus docetaxel, and BSC, the company presented the results of an indirect treatment comparison.	4.5 4.8
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.	4.8
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The committee concluded that it is plausible that nivolumab has a different level of clinical effectiveness according to PD-L1 expression.	4.7

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 the indirect comparison a reliable estimate for decision-making. Based on comments from clinical and patient experts, the committee was persuaded that nivolumab would offer some quality-of-life benefit over nintedanib because it avoids the toxicity associated with docetaxel. It also 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.	4.5, 4.8
Evidence for cost effectiveness		
Availability and nature of evidence	The committee discussed the original cost-effectiveness evidence submission presented by the company and its critique by the ERG. It accepted the structure of the economic model developed by the company.	4.9

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 • the methods used for extrapolating progression-free survival • utility values used in the model for the progression-free and progressed-disease health states • duration of the continued benefit of nivolumab • application of a 2-year clinical stopping rule.	4.10 to 4.13 4.11, 4.14, 4.18, 4.19, 4.20 4.21

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 selection bias could 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. The committee considered that the company's originally estimated utility values for the progressed-disease health state (based on CheckMate 057) may be overestimated due to selection bias, and the ERG's utility value may be underestimated due to the source study. It noted that in its final revised modelling, the company changed the utility values and applied the committee's preferred values. Therefore, utility values of 0.713 and 0.569 were used for the progression-free and progressed-disease health states respectively. 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 quality-adjusted life year calculations.	4.18 4.18, 4.19 4.27

Are there specific groups of people for whom the technology is particularly cost effective?	The committee considered that the cost-effectiveness results presented by the company for the subgroup analyses were unreliable and were not suitable for decision-making. Nivolumab has shown no convincing overall survival benefit versus docetaxel for patients whose tumours were PD-L1 negative or whose PD-L1 level was not quantifiable in the clinical evidence presented to it, the committee considered it reasonable to exclude those patients from the cost-effectiveness considerations.	4.32 to 4.33
What are the key drivers of cost effectiveness?	The committee noted that the approaches used by the company and the ERG to extrapolate overall survival had a major effect on the results of the economic model.	4.12

Most likely cost-effectiveness estimate (given as an ICER)	The committee took into account the company's further new analysis which included a 3-year data cut from CheckMate 057, a new commercial access agreement and new clinical data. It concluded that nivolumab had shown plausible potential for cost effectiveness for the subgroup of patients with PD-L1-positive tumours compared with docetaxel and with nintedanib plus docetaxel. It therefore recommended nivolumab for treating locally advanced or metastatic non-squamous NSCLC in adults after chemotherapy for use within the Cancer Drugs Fund, only if their tumours are PD-L1 positive and the conditions of the managed access agreement are followed. For nivolumab compared with BSC, the committee was not able to make a recommendation because it has not been presented with cost-effectiveness results for this population.	4.30 to 4.35 4.25
Additional factors taken into account		
Patient access schemes (PPRS)	There is a patient access scheme for nintedanib which is a confidential simple discount. The committee noted that the company had proposed a revised patient access scheme for nivolumab which was replaced with a managed access agreement. The financial terms of the agreement are commercial in confidence.	2

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.	4.26
Equalities considerations and social value judgements	No equality issues were identified.	–
Cancer Drugs Fund	The committee concluded that nivolumab met the criteria to be considered for inclusion in the Cancer Drugs Fund, and recommended nivolumab as an option for use within the Cancer Drugs Fund.	4.28 to 4.35

5. Implementation

5.1 When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a patient has previously treated non-squamous non-small-cell lung cancer and the doctor responsible for their care thinks that nivolumab is the right treatment, it should be available for use, in line with NICE's recommendations and the Cancer Drugs Fund criteria in the managed access agreement. Further information can be found in NHS England's Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry.

5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance when the drug or treatment, or other technology, is approved for use within the Cancer Drugs Fund. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, for use within the Cancer Drugs Fund, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal determination or agreement of a managed access agreement by the NHS in Wales, whichever is the latter.

5.3 Nivolumab has been recommended according to the conditions in the managed access agreement. As part of this, NHS England and Bristol–Myers Squibb have a commercial access agreement that makes nivolumab available to the NHS at a reduced cost. The financial terms of the agreement are commercial in confidence. Any enquiries from NHS organisations about the commercial access agreement should be directed to [NICE to add details at time of publication]

6. Review of guidance

6.1 The data collection period is expected to end in June 2019, when 5-year overall survival data from the CheckMate 057 clinical trial is available. The process for exiting the Cancer Drugs Fund will begin at this point and the review of the NICE guidance will start.

6.2 As part of the managed access agreement, the technology will continue to be available through the Cancer Drugs Fund after the data collection period has ended and while the guidance is being reviewed. This assumes that the data collection period ends as planned and the review of guidance follows the standard timelines described in the addendum to NICE's methods and processes when appraising cancer technologies.

Andrew Stevens
Chair, appraisal committee
September 2017

7. 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 1 or more health technology analysts (who act as technical leads for the appraisal) and a project manager.

Henry Edwards, Boglarka Mikudina
Technical Leads

Alexandra Filby
Technical Adviser

Steph Yates
Project Manager

ISBN: [to be added at publication]