NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Nivolumab for previously treated locally advanced or metastatic 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 7.

1 Recommendations

1.1 Nivolumab is not recommended for treating locally advanced or metastatic 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 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 £2,634 per dose, and £5,268 per month, for a person weighing 73 kg. Costs may vary in different settings because of negotiated procurement discounts. The company has proposed a patient access scheme to 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 does not constitute an excessive administrative burden on the NHS.

3 Evidence

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.

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 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.

Clinical management of the condition

4.1 The committee discussed the management of squamous NSCLC in clinical practice, and, in doing so, considered the most relevant comparators for nivolumab in this appraisal. The committee was aware that the marketing authorisation for nivolumab and the NICE scope for this appraisal are for people who have had previous chemotherapy, and that its recommendations are only for this population. It understood that squamous NSCLC is most commonly treated first with platinum combination chemotherapy, followed by docetaxel if the disease progresses or relapses and then best supportive care if there is a further relapse or progression. The committee was aware that erlotinib might be considered after platinum combination chemotherapy for some people, but that this is relatively rare. The committee was also aware that docetaxel is not suitable for all people whose disease relapses after platinum combination chemotherapy; it understood that in this case, the disease is usually managed with best supportive care.

4.2 In light of the current management of the condition, the committee discussed the most appropriate comparators for nivolumab within its marketing authorisation for squamous NSCLC. It noted that the scope for the appraisal included docetaxel, erlotinib and best

supportive care as potential comparators. Because erlotinib is only rarely used in this setting, the committee considered that treatment with erlotinib should not be considered established clinical practice and that it was not a relevant comparator. The committee considered whether best supportive care should be considered a comparator. It heard from the clinical experts that nivolumab was likely to be considered as an option for people with relapsed squamous NSCLC for whom docetaxel is also an appropriate option. The committee reasoned that if docetaxel were an appropriate treatment option, it would be given in preference to best supportive care. The committee therefore considered that best supportive care would not be routinely used for people who have had treatment with platinum combination chemotherapy and for whom docetaxel is also an appropriate option, and so was not an appropriate comparator in this patient population. The committee was aware that the marketing authorisation for nivolumab for squamous NSCLC is not restricted to treatment after only 1 line of chemotherapy, but may also be used after more than 1 previous treatment. In this circumstance, best supportive care may be an appropriate comparator. However, the committee heard that the number of people who have best supportive care after 2 previous lines of chemotherapy is small. It therefore considered that best supportive care should not be considered an appropriate comparator in this setting. The committee concluded that the most appropriate comparator for nivolumab for treating squamous NSCLC after previous chemotherapy is docetaxel.

Nature of the condition

4.3 The committee noted that squamous NSCLC causes distressing symptoms, which are difficult to manage. It heard from a patient expert that people with this disease often have comorbidities and poor quality of life. The committee was aware that docetaxel is

often not well tolerated, and noted comments received during consultation stating that there are few alternative treatments for squamous NSCLC. The committee concluded that there is an important unmet need for people with squamous NSCLC whose disease has progressed after chemotherapy.

Clinical effectiveness

4.4 The committee noted that the key clinical-effectiveness evidence for nivolumab compared with docetaxel was taken from the CheckMate-017 trial, and that the company also presented indirect treatment comparisons for nivolumab compared with erlotinib and best supportive care. It recalled that the most appropriate comparator for nivolumab was docetaxel (see section 4.2), and understood that both the company and the evidence review group (ERG) considered the indirect comparisons unreliable; the committee therefore did not discuss the indirect comparisons further, and focused on the evidence from CheckMate-017. The committee highlighted that, compared with docetaxel, nivolumab provided statistically significant gains in both median overall survival (a gain of 3.2 months) and median progression-free survival (a gain of 0.7 months). The clinical experts reported seeing dramatic benefits with nivolumab in clinical practice, consistent with the clinical trial results. Whereas chemotherapy is considered to slow the rate of disease progression, nivolumab may provide long-term disease stabilisation and allow some people to return to normal life. The clinical experts also said that although long-term survival evidence is not yet available, it was likely that there would be people who would gain a long-term survival benefit with this treatment. The committee also noted comments received during consultation, which emphasised that nivolumab is a valuable and clinically-effective treatment option. Based on the gains in overall

and progression-free survival seen in the CheckMate-017 trial, and taking into account the clinical experts' statements and the consultation comments, the committee concluded that nivolumab is a clinically-effective treatment option for previously treated squamous NSCLC.

4.5 The committee heard from the clinical experts that the patient population in CheckMate-017 was likely to closely reflect people for whom nivolumab would be considered in clinical practice. The committee was aware of the ERG's concerns that people with a worse Eastern Cooperative Oncology Group (ECOG) performance status were excluded from the trial, but was reassured by the clinical experts that people in this situation would be unlikely to have nivolumab in clinical practice. The committee therefore concluded that the results of CheckMate-017 are generalisable to clinical practice in England.

4.6 The committee noted that the company presented pre-specified subgroup analyses from CheckMate-017, based on patient and disease characteristics and the proposed biological marker (PD-L1 expression). The committee noted that the marketing authorisation for nivolumab does not specify PD-L1 mutation expression. However, clinical-effectiveness data for subgroups by PD-L1 expression were presented by the company in the EPAR (that is, PD-L1 expression of 1% or more compared with less than 1%, 5% or more compared with less than 5%, and 10% or more compared with less than 10%). It noted that people treated with nivolumab whose PD-L1 expression level was above a threshold of 1% or more had a higher median overall survival (9.3 months) than those with a PD-L1 expression below the threshold (8.7 months). It also noted that as the threshold was raised to 5% or more, the median overall-survival also increased for those with a PD-L1 expression

above the threshold (10.0 months) compared with people whose PD-L1 expression was below 5% (8.5 months). This suggested to the committee that nivolumab becomes more effective as the level of PD-L1 expression rises. The committee noted that when the threshold was increased to a PD-L1 expression of 10%, patients having nivolumab and whose PD-L1 expression was 10% and above had a median overall survival of 10.6 months, whereas those with an expression below 10% had a median overall survival of 8.2 months. The committee 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 did not present 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. Therefore, it would have expected the company to present an analysis using a PD-L1 expression threshold, particularly the 10% threshold because treatment with nivolumab seems to markedly improve the median overall survival of patients with higher PD-L1 expression.

Cost effectiveness

4.7 The committee considered the cost-effectiveness evidence presented by the company throughout the appraisal and the exploratory analyses presented by the ERG. It heard that the ERG considered the model to be appropriately structured and implemented to a good standard. The committee considered the company's model in detail, and discussed 3 key areas of concern about the company's approach: the extrapolation of progression-

free survival and overall survival, the utility scores, and the duration and costs of treatment.

4.8 The committee noted that the company's and the ERG's revised patient access scheme (PAS) analyses were based on updated data for progression-free survival, overall survival and time to discontinuation, with up to 18 months of follow-up. It considered that it was appropriate to use the latest evidence in the economic model, and therefore concluded that the results from the revised PAS analyses were most relevant for decision-making.

Extrapolation of progression-free and overall survival

4.9 The committee understood that the company's and the ERG's revised PAS analyses incorporated the committee's preferred approach to extrapolating progression-free survival beyond the point at which data from the trial were available. In this approach, extrapolation of the data began from the time at which the nivolumab and docetaxel curves began to diverge (2.2 months). The committee understood that the ERG proposed this approach because it considered that using the full dataset could have led to the early section of the curves over-influencing the long-term extrapolation. The ERG highlighted that the first radiological assessment of tumour progression in the trial only occurred after 3 months of treatment. Before this point, the progression-free-survival curves for nivolumab and docetaxel were very similar, potentially masking the true treatment effect during this time period. The committee understood that the company agreed with this approach after consultation, and that the company and ERG both used the same approach in their revised PAS analyses. The committee therefore concluded that the extrapolation of progression-free survival in the revised analyses was appropriate.

4.10 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, and were a key difference between the company's analyses and the ERG's exploratory and revised analyses. The committee noted that the company used the log-logistic function and fitted the data from CheckMate-017 to extrapolate overall survival in its original base case.

4.11 The committee discussed several uncertainties in the clinical plausibility of the results predicted by the company's extrapolation of overall survival.

- It noted that the company's modelling predicted substantial overall-survival gains associated with nivolumab beyond 2 years; it was aware that this was in the extrapolated part of the model, and so was subject to uncertainty.
- The committee noted that the company emphasised that its extrapolation matched the longer-term survival results seen in the CheckMate-003 trial. However, the committee considered that the CheckMate-003 trial was a limited source of corroboration, because it was a single-arm trial including people with either squamous or non-squamous NSCLC and had a small population size at later time points. Furthermore, the committee noted that the ERG's less-optimistic extrapolation (see sections4.9) was also consistent with the CheckMate-003 trial findings. The committee therefore considered that this study could not support 1 approach above the other.
- It noted that most of the overall-survival gain was accrued after disease progression when treatment with nivolumab had stopped, suggesting a long benefit after treatment that is greater than the benefit during treatment. The committee heard that in the ERG's analysis of post-progression survival, there was no

apparent difference between nivolumab and docetaxel in CheckMate-017. It was aware that the company believed that there were limitations in this analysis, because the company considered that there was selection bias and limited follow-up in the analysis; however, the committee agreed with the ERG that the analysis was the best available with present data. The committee concluded that this analysis highlighted that the CheckMate-017 trial did not provide evidence for a dramatic gain in survival after disease progression with nivolumab compared with docetaxel. The committee considered, based on comments from the clinical experts and the company, that some gain in survival after disease progression would be plausible and would be consistent with the mechanism of action of nivolumab; however, it concluded overall that the size of the gain implied by the company's model was neither plausible nor supported by the clinical-trial evidence.

- The committee also understood that the model predicted that mortality risk would decrease over time. It recalled that the company considered this appropriate, and understood its explanation (see section 4.9). The committee considered that a decreasing mortality risk over time could potentially be justified, but the size of the decrease in the company's model was highly uncertain. The committee was aware that the company's revised analysis included a 'cap' on the mortality risk, so that it did not drop below the level in the general population. It considered that this cap mitigated an implausible aspect of the company's original model, but the need for the cap implied that the log-logistic approach may be unsuitable for modelling overall survival in this case.

The committee concluded that there were important uncertainties in the results predicted by the log-logistic approach.

4.12 The committee therefore considered the ERG's exploratory analysis of overall survival. It understood that the ERG considered that the results of its approach were a good fit to the data from the CheckMate-017 evidence and fell within the 95% confidence intervals of 3-year overall-survival data from CheckMate-003 (although the committee noted that this trial was a limited source of corroboration; see section 4.11). The committee heard from the ERG that an exponential function is consistent with the survival trend seen in this long-term follow-up of a cohort of people with NSCLC. It also understood that, as in the results of the company's analysis, the ERG's analysis predicted a survival gain after disease progression; however, it noted that this gain was both smaller in size and a smaller proportion of the total overall-survival gain than predicted by the company. The committee recalled its consideration that a gain in survival after disease progression would be plausible and would be consistent with the mechanism of action of nivolumab, but that the size of gain predicted by the company was not plausible (see section 4.11), and so considered that the ERG's analysis appeared to mitigate some of the limitations in the company's results. The committee therefore concluded that the ERG's modelling of overall survival using the exponential model was more appropriate for its decision-making.

4.13 The committee noted that in its revised PAS base case, the company used a 2-knot spline model to extrapolate overall survival. This suggested to the committee that there are 3 heterogeneous subgroups of patients, each with a different survival profile that can be expressed as a combination of 3 curves. The committee was not persuaded that this was a better prediction of overall survival in these patients than the ERG's approach.

Utility values

4.14 The committee noted that the company had collected evidence on quality of life using the EuroQol EQ-5D questionnaire in the CheckMate-017 trial, and that it had used utility scores based on these data in the model. It noted that in the company's original base case, the utility values in the progression-free and progressed-disease health states were 0.750 and 0.592 respectively. However, the committee noted limitations in this evidence. It considered that the negative correlation between EQ-5D score and the number of respondents strongly suggested that the results were influenced by selection bias, that is, the people who completed the EQ-5D (particularly at later time points) were not representative of the wider population. The committee also noted the substantial increase in EQ-5D over time. Although the committee understood that the company had used averages to calculate health-state utility values (and not time-dependent utilities) to avoid too much influence from the later results, it considered that the changes over time hadn't been fully explained and cast further doubt on the validity of the EQ-5D data in CheckMate-017. The committee was aware that the utility values used in the company's model were higher than corresponding utilities in other lung cancer appraisals. For example, in NICE's technology appraisal of erlotinib and gefitinib for non-small-cell lung cancer the utility values in the progression-free and progressed-disease health states were 0.62–0.65 and 0.47 respectively. The committee discussed the alternative utility values used in the ERG's exploratory analysis. It noted that these alternative utility values were 0.65 in the progression-free health state and 0.43 in the progressed-disease health state, and considered that these values had greater face-validity than those presented by the company. However, it was also aware of limitations in how the

ERG's utility values had been derived – in particular, that they were based on standard gamble methods rather than time trade-off. The committee considered that there were limitations in the utility values presented by both the company and the ERG. It acknowledged that the company's values of 0.750 and 0.592 (progression-free and progressed-disease health states respectively) were taken from EQ-5D data in the CheckMate-017 trial but considered that they were likely to have been overestimated; on the other hand, the ERG's values (0.65 and 0.43) were lower, but there were limitations in how they were derived. The committee concluded that it would be reasonable to consider that the most appropriate values would be between those presented by the company and those from the ERG.

4.15 The committee considered the alternative health-state utility values presented in the ERG's revised PAS analyses. For the progression-free health state, the committee noted that the utility values presented by the ERG were based on EQ-5D data from CheckMate-017 and were consistent with its considerations on the company's original analysis and the ERG's exploratory analysis. The committee therefore considered that a utility value of 0.693 in the progression-free health state would be appropriate for decision-making. For the progressed-disease health state, the committee highlighted that the ERG had included a decrease in quality of life as people neared the end of life, by reducing the health-state utility score; it calculated that the ERG had used a utility reduction of 0.085. It considered that this was an important advantage of the ERG's approach. The committee noted that adjusting the company's revised utility value to take into account the decrease in quality of life at the end of life would give a value of 0.509, which was consistent with the committee's considerations on the company's original analysis and the ERG's exploratory analysis.

Given that the company's revised analysis used EQ-5D data from CheckMate-017, the committee concluded that it would be reasonable to use a utility value of 0.509 in the progressed-disease health state for decision-making.

4.16 The committee noted that the company had taken the utility decrements associated with adverse effects from external sources, rather than CheckMate-017. The committee acknowledged that there were limitations in the data available from the trial, but stressed that the company's approach was inconsistent with its approach for the health-state utilities. The committee was reassured by the clinical experts that the most important adverse effects had been included in the company's analysis, and also understood that the adverse-effect disutilities were unlikely to have an important effect on the economic model results. It concluded that adverse effects had been adequately captured in the model.

Duration and costs of treatment

4.17 The committee discussed the duration of treatment in the company's economic model. It noted that in CheckMate-017, some people were treated with nivolumab after disease progression (consistent with the trial protocol). The committee understood that the company had estimated the duration of treatment based on the assumption that people continued only until their disease progressed, and therefore treatment beyond progression had not been included in the company's model. The committee considered that if it were, the costs associated with nivolumab would increase. At the same time, the committee noted that the ERG's exploratory analysis based on time to treatment discontinuation data from CheckMate-017 accounted for treatment beyond progression as well as stopping because of adverse events. The committee noted that the company stated in response to consultation that

progression-free survival could be considered a suitable proxy measure for the duration of treatment. It noted that the company highlighted the similarity between the progression-free-survival and time to discontinuation curves. The committee considered that because time to treatment discontinuation data from CheckMate-017 were available, it would be appropriate to use them in the economic model. The committee concluded that because the ERG had used the treatment duration data from the trial (which was consistent with the effectiveness data from the trial) and had properly captured treatment beyond progression as well as stopping because of adverse events, the ERG's approach to modelling treatment duration was more appropriate.

4.18 The committee noted the ERG's comment that in clinical practice, docetaxel therapy is usually limited to a maximum of 4 cycles, and so the economic model should also be limited to a maximum of 4 cycles. However, the committee was aware that the duration of docetaxel therapy was not limited in CheckMate-017, and so considered that applying such a limit would lead to inconsistency between the costs and clinical outcomes in the economic model. The committee concluded that the approach of not limiting docetaxel to a maximum of 4 cycles in the economic model – used in the company's original and revised PAS analyses and the ERG's revised analysis – was appropriate in this case.

4.19 The committee considered the scenario analyses presented by the company, in which the duration of nivolumab treatment was limited to a maximum of 2 years. It heard from the company that the mechanism of action of nivolumab suggested that its effects on tumours would continue after treatment stopped. It also heard that the optimum duration of treatment with immunotherapies such as nivolumab is uncertain and is an area of debate among clinicians; it

understood that clinicians may stop treatment after 6 months to 2 years, although there is no consensus. The committee considered that it was biologically plausible that the effects of nivolumab may continue after treatment stops, and that in clinical practice, clinicians might stop treatment after 2 years. However, the committee was concerned that there was very limited evidence to support this approach. In particular, CheckMate-017 (on which the clinical outcomes in the economic model were based) did not include a maximum duration. The committee agreed that applying a maximum treatment duration would lead to inconsistency between the costs and clinical outcomes in the economic model, and emphasised that the company's assumption that the clinical outcomes would be the same as in the trial with a 1- or 2-year maximum duration was not proven and not sufficiently evidence based. The committee concluded that it was unable to make recommendations based on a maximum treatment duration of nivolumab therapy.

4.20 The committee understood that the company was carrying out a clinical trial (CheckMate-153) in which the effect of a 1-year maximum treatment duration was being studied, 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 therefore improve its cost effectiveness. The committee was aware that a 2-year stopping rule was not included in the summary of product characteristics and reasoned that it was unlikely that clinicians would adhere to a stopping rule that was 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 about the application of a stopping rule in clinical practice and the assumption should not be applied to the economic modelling.

4.21 The committee noted that, in its original analysis, the company had estimated drug costs based on a single average body weight and surface area, used the list prices for generic drugs, and assumed different administration costs for nivolumab and docetaxel. It heard that the ERG considered that it would be more appropriate to use distributions for body weights and surface areas and the average NHS costs for generic medicines (based on data from the Commercial Medicines Unit's Electronic Market Information Tool [eMIT]), and that it was not necessary to use different administration costs. The committee agreed with the rationale for the ERG's approach and so considered that the ERG's exploratory analyses and the company's and the ERG's revised PAS analyses, in which the preferred approaches for these assumptions were used, were appropriate.

Conclusions on cost effectiveness

4.22 The committee considered all the ICERs for nivolumab compared with docetaxel presented by the company and the ERG in which the PAS had been incorporated. It noted that these were all above £66,100 per QALY gained (company's deterministic revised PAS ICER), with the lowest estimate provided by the company and the highest by the ERG (£73,500 per QALY gained). Unlike the company's revised PAS base case, the ERG's exploratory analysis included all of the committee's preferred assumptions. It understood that the main difference between these estimates was the ERG's correction of the application of the 2-knot spline model in the overall-survival extrapolation. Taking into account that not all of the committee's preferred assumptions were included in the company's revised PAS base case, the committee concluded that the most plausible ICER for nivolumab compared with docetaxel would be at least £73,500 per QALY gained.

End-of-life considerations

4.23 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 advanced or metastatic NSCLC have a life expectancy of less than 24 months. It understood that the median overall-survival gain associated with nivolumab in CheckMate-017 was more than 3 months, and that the mean overall-survival gains predicted by the company's and the ERG's economic analyses were both much more than 3 months (15.7 months and 7.17 months respectively). The committee was therefore convinced that nivolumab provides an extension to life greater than 3 months compared with current treatment. The committee noted that the company estimated that nivolumab would be indicated for 853 people with squamous NSCLC in England. It was aware that nivolumab also has a marketing authorisation for treating advanced (unresectable or metastatic) melanoma in adults. The committee considered that, taking into account both squamous NSCLC and melanoma, nivolumab was indicated for a small patient population. The committee was persuaded that the estimates of the extension to life were robust and that the assumptions used in the economic modelling were plausible, objective and robust. The committee therefore concluded that nivolumab met the criteria to be considered a life-extending, end-of-life treatment.

Innovation

4.24 The committee heard from the company, clinical experts, patient experts and consultees that they consider nivolumab to be an innovative treatment option, both in its therapeutic approach and its clinical effectiveness. It understood that before the marketing

authorisation was granted, nivolumab was available through the early access to medicines scheme. It also noted that there are limited alternative treatments for this condition. The committee concluded that nivolumab is innovative, but there were no additional benefits associated with this treatment that had not been captured in the economic analysis.

Pharmaceutical Price Regulation Scheme (PPRS) 2014

4.25 The committee was aware of NICE's position statement about 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 of nivolumab. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of nivolumab for treating locally advanced or metastatic squamous NSCLC after prior chemotherapy.

Cancer Drugs Fund

4.26 The committee considered whether nivolumab for locally advanced or metastatic 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).

4.27 The committee agreed that the ICERs for the full licensed population did not indicate a plausible potential for cost effectiveness (see section 4.22). 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 4.6). 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 4.19) 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 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.

4.28 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.

4.29 In summary, the committee concluded that nivolumab for previously treated locally advanced or metastatic 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 squamous non-small-cell lung cancer	Section
Key conclusion		
Nivolumab for previously treated locally advanced or metastatic squamous non-small-cell lung cancer is not recommended for routine use in the NHS because it has not been shown to be cost effective. The committee is minded not to recommend nivolumab for a subgroup of people with PD-L1 expression of at least 10% for inclusion in the Cancer Drugs Fund, as no estimates of cost effectiveness have been presented for this subgroup. However the committee invites the company to submit a proposal for inclusion in the Cancer Drugs Fund for this subgroup.		1.1, 4.28
Current practice		
Clinical need of patients, including the availability of alternative treatments	The committee noted that squamous NSCLC causes distressing symptoms and people with this disease often have poor quality of life. It was aware that docetaxel is often not well tolerated, and that there are few alternatives. The committee concluded that there is an important unmet need for people with squamous NSCLC whose disease has	4.3

	progressed after chemotherapy.	
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 and patient experts that they consider nivolumab to be innovative, both in therapeutic approach and clinical effectiveness. Before the marketing authorisation was granted, nivolumab was available through the early access to medicines scheme; a positive opinion was later granted by the UK Medicines and Healthcare products Regulatory Agency.	4.24
What is the position of the treatment in the pathway of care for the condition?	The committee was aware that the marketing authorisation for nivolumab and the NICE scope for this appraisal are for people who have had previous chemotherapy (including after 1 line of chemotherapy or after more than 1 previous treatment). The clinical experts stated that nivolumab was likely to be considered as an option for people with relapsed squamous NSCLC for whom docetaxel is also an appropriate option.	4.2
Adverse reactions		
Evidence for clinical effectiveness		
Availability, nature	The company presented evidence from	4.4,

and quality of evidence	1 randomised controlled trial (CheckMate-017) ~~and non~~and non-randomised trials (CheckMate-003 and -153).	4.11, 4.20
Relevance to general clinical practice in the NHS	The committee understood that the patient population in CheckMate-017 was likely to closely reflect people for whom nivolumab would be considered in clinical practice, and concluded that the results are generalisable to clinical practice in England.	4.5
Uncertainties generated by the evidence	The committee noted noted that the company did not present any further evidence of the clinical effects in different subgroups of people according to their level of PD-L1 expression.	4.6
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	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. The committee concluded that although it is plausible that nivolumab might have a different level of clinical effectiveness according to PD-L1 expression, it had not been presented with any additional evidence to consider these subgroups separately.	4.6

Estimate of the size of the clinical effectiveness including strength of supporting evidence	Nivolumab was associated with statistically significant improvements in overall-survival, progression-free survival and overall-response rates, compared with docetaxel. The median overall-survival gain with nivolumab in the trial was 3.2 months, and the mean gains predicted by the company's and the ERG's economic analyses were both much more than 3 months (15.7 months and 7.17 months respectively).	4.4
Evidence for cost effectiveness		
Availability and nature of evidence	The company presented an economic model comparing nivolumab with docetaxel, in people with locally advanced or metastatic squamous NSCLC that had progressed during or after treatment with 1 platinum combination chemotherapy. The committee noted that the company's and the ERG's revised analyses were based on updated data for progression-free survival, overall survival and time to discontinuation, with up to 18 months of follow-up. It considered that it was appropriate to use the latest evidence in the economic model.	4.7 – 4.8
Uncertainties around and plausibility of assumptions and inputs in the	The committee considered the following key areas of uncertainty: • the methods used for extrapolating	4.9– 4.21

economic model	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 • application of a 2-year clinical stopping rule	
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 company estimated quality of life by applying utility values to the progression-free and progressed-disease health states (0.750 and 0.592 respectively), derived from EQ-5D utility-index data collected in CheckMate-017. The committee concluded that it would be reasonable to use utility values of 0.693 (progression-free health state) and 0.509 (progressed-disease health state) for decision-making. The committee considered that there were no additional benefits associated with nivolumab that had not been captured in the economic analysis.	4.14 – 4.15 4.24

Are there specific groups of people for whom the technology is particularly cost effective?	None, although the committee concluded that nivolumab has the potential for being cost effective in those people with a PD-L1 expression of at least 10%.	4.6 4.26
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, and were a key difference between the company's analyses and the ERG's exploratory and revised analyses.	
Most likely cost-effectiveness estimate (given as an ICER)	The committee concluded that the most plausible incremental cost-effectiveness ratio (ICER) for nivolumab compared with docetaxel, with the patient access scheme applied, was at least £73,500 per quality-adjusted life year (QALY) gained.	4.22
Additional factors taken into account		
Patient access schemes (PPRS)	There is a proposed confidential PAS discount for nivolumab.	–
End-of-life considerations	The committee noted that people with advanced or metastatic NSCLC have a life expectancy of less than 24 months. It was convinced that nivolumab provides an extension to life greater than 3 months	4.23

	compared with current treatment. The committee noted that nivolumab would be indicated for a small patient population. The committee was persuaded that the estimates of the extension to life were robust and that the assumptions used in the economic modelling were plausible, objective and robust. The committee concluded that nivolumab met the criteria to be considered a life-extending, end-of-life treatment.	
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

ISBN: [to be added at publication]

6 Appraisal committee members, guideline representatives and NICE project team

Appraisal committee members

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

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Ian Watson and Richard Diaz
Technical Leads

Joanne Holden
Technical Adviser

Lori Farrar and Stephanie Yates
Project Managers

ISBN: [to be added at publication]