NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance

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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

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

- 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. The pricing arrangement considered during guidance development was that the company had agreed a patient access scheme with the Department of Health. This scheme would provide a simple discount to the list price of nivolumab with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS. The managed access agreement agreed between the company and NHS England will replace this patient access scheme.

3 Evidence

3.1 The appraisal committee (section 6) 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 (ERG) 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 appraisal committee at the fifth meeting. See the committee papers for full details of the evidence.

3.2 Sections 4.1 to 4.26 reflect the committee's discussion of the evidence submitted for the first to fourth appraisal committee meetings. Section 4.27 (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 4.33 and 4.34.

4 Committee discussion

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

4.2 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.

Comparators

4.3 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 was not established clinical practice and that it was not a relevant comparator. The committee discussed whether best supportive care is a possible 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 an appropriate option, and so best supportive care was not an appropriate comparator in this patient population. The committee concluded that the most appropriate comparator for nivolumab for treating squamous NSCLC after previous chemotherapy was docetaxel.

Nature of the condition

4.4 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 that there are few alternative treatments for squamous NSCLC. The committee noted 2 petitions, received during consultation, highlighting patients' desire for another treatment option. The committee concluded that there is an important unmet need for people with squamous NSCLC whose disease has progressed after chemotherapy.

Clinical effectiveness

Clinical-trial data

4.5 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 4.3), 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 allow long-term disease stabilisation so that some people can return to normal life. The committee noted the company provided more mature data cuts from the clinical trials (CheckMate 003, 5-year cut; CheckMate 017, 3-year cut). However these results were very similar to the results from the earlier data cuts. The clinical experts also said that although long-term survival evidence is not yet available, it was likely that some people would gain a long-term survival benefit with this treatment. The committee noted comments received during the first consultation, which emphasised that nivolumab is a valuable and clinically effective treatment option. It also noted the comments from the second consultation that nivolumab would be an effective and useful 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.

PD-L1 expression

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 (programmed death cell ligand-1 [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 European Public Assessment Report (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 who had nivolumab, and 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 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 noted comments from the consultation on the second appraisal consultation document that it was inappropriate to make a recommendation based on PD-L1 because it is a heterogeneous biological marker.The committee considered further new clinical evidence submitted by the company in its final decision-making, which is discussed in sections 4.29 to 4.34.

4.7 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 these people 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.

Cost effectiveness

4.8 The committee discussed the cost-effectiveness evidence presented by the company and its critique by the ERG. It accepted the structure of the economic model developed by the company. The committee noted its recommendation in the second appraisal consultation document, for people with a PD-L1 expression of at least 10%, 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, and instead continued with an alternative, but new, proposal for the whole population.

4.9 The committee was aware that the company's new proposal included the use of an 'intermediary', overall-survival 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 thesecond 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 DSU produced its report. It noted that the company's new evidence included a new (3-year) data cut from CheckMate 017 and CheckMate 003.

Extrapolation of progression-free survival

4.10 The committee understood that after the consultation on the first appraisal consultation document, the ERG's revised 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 data collected in the early stages of the trial over-influencing the long-term extrapolation. The ERG highlighted that the first radiological assessment of tumour progression in the trial was only 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 the first consultation. The committee was aware that after the second appraisal consultation document, the company presented new evidence and suggested using alternative approaches to extrapolate progression-free survival. It noted that the alternative approaches to extrapolation 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 the committee saw no reason to change its previously agreed approach of using the exponential curve after the observed trial data splits. The committee therefore concluded that the most appropriate approach to extrapolating progression-free survival was using trial data until 2.2 months and then applying an exponential curve for extrapolating up to the full time horizon of the model.

Extrapolation of overall survival

4.11 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 after the first appraisal consultation document. The committee noted that the company used the data from CheckMate 017 and fitted a log-logistic curve to extrapolate overall survival in its original base case. 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 there was likely to be uncertainty about the results.
- 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 was aware that the results of the CheckMate 003 trial should be interpreted with caution 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.
- It noted that most of the overall-survival gain happened 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 did not seem to be any 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 this was the best analysis given the available evidence. The committee concluded that this analysis highlighted that the CheckMate 017 trial did not offer 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. 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. The committee considered that this cap lessened an implausible aspect of the company's original model, but the need for the cap implied that the original log-logistic extrapolation method was unsuitable for modelling overall survival in this case.

  Therefore, the committee concluded that there were important uncertainties in the results predicted by the company's log-logistic approach.

4.12 The committee 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 CheckMate 017 data and fell within the 95% confidence intervals of 3-year overall-survival data from CheckMate 003. 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 in the 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 consistent with the mechanism of action of nivolumab. But the size of gain predicted by the company was not plausible (see section 4.11), and so it considered that the ERG's analysis seemed to reduce some of the limitations in the company's results. The committee therefore agreed that the ERG's modelling of overall survival using the exponential model was more appropriate for its decision-

making.

4.13 After the consultation on the second appraisal consultation document and receiving the new evidence and 'intermediary' overall-survival curve proposed by the company for the whole population, NICE commissioned the DSU to explore the goodness of fit for all overall-survival extrapolation curves, and propose a preferred curve fit (see section 4.9).The committee understood that the DSU based its report on the 2-year data cut from CheckMate 017 and a 4-year data cut from CheckMate 003. The committee noted that the DSU's report suggested that the evidence supported using a decreasing hazards function, and that an 'intermediary' curve, using a generalised gamma curve (suggested by the company in their new evidence submission after consultation on the second appraisal consultation document), was a plausible method for overall-survival extrapolation.

4.14 The committee also considered new evidence from the company (more mature data cuts from CheckMate 017 at 3 years and CheckMate 003, at 5 years) and noted that the company had proposed a revised patient access scheme. It heard from the company that this more mature data cut continued to support using the log-logistic curve for extrapolating overall survival. The committee heard from the DSU that after reviewing the new evidence, they were still confident that the generalised gamma curve was the most appropriate. The DSU highlighted that there was a lot of uncertainty about the tail of the overall-survival extrapolation from the trial data because of the small number of people still alive at 36 months (21 people). It further noted that the log-logistic and generalised gamma curves provided very similar fits to the trial data. The committee heard from the company that the difference in Akaike information criterion (AIC) and Bayesian information criterion (BIC) between these curves was small. The committee, noting the new evidence and the DSU's expert advice, concluded that the overall-survival extrapolation was uncertain but the DSU's approach (intermediary, generalised gamma curve) was the most appropriate because the tail of the curve more closely reflected the likely continued treatment effect.

Utility values

4.15 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 the 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) did not represent 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 increased doubt about 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 NSCLC, the utility values in the progression-free and progressed-disease health states were 0.62 to 0.65 and 0.47 respectively. The committee discussed the alternative utility values used in the ERG's exploratory analysis. It noted that these values were 0.65 and 0.43 in the progression-free and progressed-disease health states respectively, 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 the most appropriate values were likely to be between those presented by the company and those by the ERG.

4.16 The committee considered the alternative health-state utility values presented in the ERG's revised analyses after the consultation on the first appraisal consolation document. For the progression-free health state, the committee noted that the ERG's utility values 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.

4.17 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.

Treatment duration

4.18 The committee discussed the duration of treatment in the company's economic model. It noted that in CheckMate 017, some people had 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 after progression as well as

stopping because of adverse events. The committee noted that the company stated in response to the first 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, the ERG's approach to modelling treatment duration was more appropriate.

4.19 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 was appropriate in this case.

Stopping rule

4.20 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 optimum duration of treatment with immunotherapies such as nivolumab is uncertain and an area of ongoing debate among clinicians, some of whom may stop treatment after 6 months to 2 years. The committee considered that clinicians might continue treatment after 2 years if the person was still having some benefit but 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 of treatment. The committee understood that the first results of the company's ongoing study (CheckMate 153) investigating the effect of a 1-year maximum treatment duration 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. The committee

was aware that a 2-year stopping rule was not included in the summary of product characteristics and queried whether clinicians would follow a stopping rule that was not specified in the summary of product characteristics, especially if the person was still benefitting from the treatment. The committee noted comments on the second appraisal consultation document that a 2-year stopping rule is acceptable to both patients and clinicians and would be implementable. The committee's concerns were eased by the assurances from NHS England and concluded that a 2-year stopping rule should be applied in the economic model.

Continued treatment effect

4.21 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 updated 36-month results from the CheckMate 017 trial, and noted that the differences between the nivolumab arm and the docetaxel arm were maintained and did not change compared with the previous data cuts. The committee agreed 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.

Treatment costs

4.22 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 different administration costs did not need to be used. 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 patient access scheme analyses, in which the preferred approaches for these

assumptions were used, were appropriate.

Cost-effectiveness results

4.23 The committee considered all the incremental cost-effectiveness ratios (ICERs) for nivolumab compared with docetaxel presented by the company in its base-case and scenario analyses. It noted that at NICE's request, the company had provided ICERs incorporating the company's and the committee's or ERG's preferred assumptions and the updated patient access scheme. The committee noted that the company's base-case cost-effectiveness results, using the 2-year data cut from CheckMate 017, included a log-logistic curve to extrapolate overall survival and a 2-year stopping rule and ranged from £49,200 to £54,200 per QALY gained, depending on the level of continued treatment effect applied. The committee noted that the company provided cost-effectiveness results including the committee's preferred assumptions for:

- extrapolating overall survival – using the 'intermediary' curve (see section 4.13)
- extrapolating progression-free survival – using the exponential curve (see section 4.10)
- utility values (see section 4.16)
- applying a 2-year stopping rule (see section 4.20)
- the treatment-effect duration – up to 3 years after stopping treatment (see section 4.21).

The committee concluded that given these assumptions, with the company's updated patient access scheme, it considered the most plausible ICER for nivolumab compared with docetaxel to be £60,882 per QALY gained (probabilistic estimate) although considerable uncertainty remained. The proposed patient access scheme was subsequently replaced with a commercial access agreement at the fifth appraisal committee meeting and the company also included overall-survival data from a 3-year data cut from CheckMate 017 (discussed in section 4.27 onwards), which resulted in an ICER of £49,982 per QALY gained. The committee noted that the ICER for nivolumab compared with docetaxel was above the range normally considered to be a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

4.24 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 proposed 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 were 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.

End-of-life considerations

4.25 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's final Cancer Drugs Fund technology appraisal process and methods. It noted the evidence presented by the company, which showed that people with locally advanced or metastatic squamous 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 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

4.26 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 in the NHS through the early access to medicines scheme. It also noted that alternative treatments for this condition are limited. 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.

Cancer Drugs Fund

4.27 Having concluded that nivolumab for locally advanced or metastatic squamous NSCLC after chemotherapy could not be recommended for routine use, the committee then considered whether it 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).

4.28 At the fourth appraisal committee meeting, the committee agreed that the ICERs for the full squamous NSCLC population (see section 4.24) did not show a plausible potential for cost effectiveness. 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 4.6). 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 squamous NSCLC 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 signalled in the second appraisal consultation document, 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.

4.29 At the fifth appraisal committee meeting, the company presented new evidence and a commercial access agreement proposal for inclusion in the Cancer Drugs Fund for the full squamous NSCLC population. The committee considered the subgroup analyses of overall survival (3-year data cut) and progression-free survival (2-year data cut) according to level of PD-L1 expression. It considered that nivolumab showed better effectiveness in the subgroups in which PD-L1 expression was positive, except in the case of the 1% threshold for which the hazard ratio showed better effectiveness with a PD-L1 expression below 1% than 1% or more. But it concluded that the results did not suggest a clinically significant difference according to PD-L1 expression.

4.30 On request, the company presented further cost-effectiveness results including subgroup analyses based on PD-L1 expression. This included the committee's preferred assumptions, the most recent overall-survival data from a 3-year data cut from CheckMate 017 and a new commercial access agreement. The committee noted that the cost-effectiveness result for the subgroup with a PD-L1 expression of 1% or more was more favourable, despite the clinical data (see section 4.29) which showed that people with a PD-L1 expression below 1% had a lower hazard ratio than people with a PD-L1 expression of 1% or more. Having concluded that it could not differentiate between subgroups of PD-L1 expression on the basis of evidence for clinical effectiveness, the committee further concluded that it would be unreasonable to do so for cost effectiveness.

4.31 Returning to cost-effectiveness estimates for the full population, 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 4.21), 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 for the full squamous NSCLC population changed to £50,014 per QALY gained.

4.32 The committee agreed that the ICERs for the full squamous NSCLC population (see sections 4.23 and 4.31) showed a plausible potential for cost effectiveness to satisfy the criteria for routine use, when additional weights were applied to QALY benefits for a life-extending treatment at the end of life (see section 4.25). The committee recognised that additional long-term survival data would reduce the clinical uncertainty and allow for a more certain cost-effectiveness estimate. The committee was satisfied that when the conditions of the commercial access agreement were applied, the cost-effectiveness estimates for the full squamous NSCLC population had shown plausible potential for being a cost-effective use of NHS resources and so it considered it reasonable to recommend nivolumab for inclusion in the Cancer Drugs Fund.

Overall conclusions

4.33 The committee recalled its earlier conclusions that the most plausible ICER for nivolumab with the updated proposed patient access scheme compared with docetaxel was not within the range normally considered cost effective (see section 4.23). It acknowledged that nivolumab met the criteria to be considered a life-extending, end-of-life treatment, and concluded that the ICER of £60,882 per QALY gained was 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 squamous NSCLC after chemotherapy in routine commissioning.

4.34 The committee took into account the company's further new analysis, which included a 3-year data cut from CheckMate 017 and a new commercial access agreement. It concluded that based on the clinical evidence presented at the fifth appraisal committee meeting it would not be reasonable to differentiate between subgroups according to PD-L1 expression, and an ICER of £50,014 per QALY gained for the full squamous NSCLC population, nivolumab had shown plausible potential for cost effectiveness. It therefore recommended nivolumab

for treating locally advanced or metastatic squamous NSCLC in adults after chemotherapy for use within the Cancer Drugs Fund, only if the conditions of the managed access agreement are followed.

Summary of appraisal committee's key conclusions

TA483	Appraisal title: Nivolumab for previously treated 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 squamous non-small-cell lung cancer (NSCLC) in adults after chemotherapy, only if: • 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. The committee noted the cost-effectiveness results including their preferred assumptions of • extrapolating progression-free survival, using the exponential curve • extrapolating overall survival, using the intermediary curve • utility values • applying a 2-year stopping rule • the treatment-effect duration, up to 3 years after stopping treatment. The committee took into account the company's further new analysis, which included a 3-year data cut from CheckMate 017 and a new commercial access agreement. It also noted that the DSU's changes resulted in an incremental cost-effectiveness ratio (ICER) of £50,014 per quality-adjusted life year (QALY) gained. It concluded that nivolumab had shown plausible potential for cost effectiveness. It therefore recommended nivolumab for treating locally advanced or metastatic squamous NSCLC in adults after chemotherapy for use within the Cancer Drugs Fund, only if the conditions of the managed access agreement are followed.	1.1, 4.10 to 4.22, 4.29 to 4.32

Current practice		
Clinical need of patients, including the availability of alternative treatments	The committee noted 2 petitions, received during consultation, highlighting patients' desire for another treatment option. It concluded that there is an important unmet need for people with squamous NSCLC whose disease has progressed after chemotherapy.	4.4
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 concluded that nivolumab is innovative, but there were no additional benefits associated with this treatment that had not been captured in the economic analysis.	4.26
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 chemotherapy, and that its recommendations are only for this population. 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, 4.3
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.	2
Evidence for clinical effectiveness		

Availability, nature and quality of evidence	The committee noted that the key clinical-effectiveness evidence for nivolumab compared with docetaxel was taken from the CheckMate 017 trial. 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 was aware that the results of the CheckMate 003 trial should be interpreted with caution 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.	4.5, 4.11
Relevance to general clinical practice in the NHS	Not an issue in this appraisal.	–
Uncertainties generated by the evidence	The committee noted the company provided more mature data cuts from the clinical trials (CheckMate 003, 5-year cut; CheckMate 017, 3-year cut). However these still did not provide much better evidence of long-term survival.	4.5
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The committee considered that nivolumab showed better effectiveness in the subgroups in which PD-L1 expression was positive, but the results did not suggest a clinically significant difference according to PD-L1 expression.	4.6, 4.29
Estimate of the size of the clinical effectiveness including strength of supporting evidence	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).	4.5
Evidence for cost effectiveness		

Availability and nature of evidence	The committee discussed the cost-effectiveness evidence presented by the company and its critique by the evidence review group (ERG). It accepted the structure of the economic model developed by the company.	4.8
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 • application of a 2-year clinical stopping rule • duration of the continued benefit of nivolumab.	4.10 to 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 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.	4.15 to 4.17

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. Having concluded that it could not differentiate between subgroups of PD-L1 expression on the basis of evidence for clinical effectiveness, the committee further concluded that it would be unreasonable to do so for cost effectiveness.	4.30
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.	4.11
Most likely cost-effectiveness estimate (given as an ICER)	The committee concluded that given its preferred assumptions, the incorporation of 3-year clinical-effectiveness data, the commercial access agreement and the DSU's corrections, nivolumab had shown plausible potential for cost effectiveness, based on an ICER of £50,014 per QALY gained.	4.31
Additional factors taken into account		
Patient access schemes (PPRS)	The committee noted that the company had proposed a revised patient access scheme 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 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 compared with current treatment. 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.	4.25
Equalities considerations and social value judgements	No equality issues were raised.	–

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.	4.27 to 4.32

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 of the managed access agreement. This means that, if a patient has previously treated locally advanced or metastatic 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.

6 Appraisal committee members and NICE project team

Appraisal committee members

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

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

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

NICE project team

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

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Accreditation