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, and 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 draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 9) and the public. This document should be read along with the evidence base (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 provisional 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 the Guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 19 January 2016

Second Appraisal Committee meeting: 10 February 2016

Details of membership of the Appraisal Committee are given in section 8, and a list of the sources of evidence used in the preparation of this document is given in section 9.

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

1 Appraisal Committee's preliminary recommendations

1.1 Nivolumab is not recommended within its marketing authorisation for treating locally advanced or metastatic squamous non-small-cell lung cancer after prior chemotherapy in adults.

1.2 People whose treatment with nivolumab was started within the NHS before this guidance was published should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 The technology

2.1 Nivolumab (Opdivo, Bristol-Myers Squibb) is a monoclonal antibody that targets a receptor on the surface of lymphocytes known as PD-1. This receptor is part of the immune checkpoint pathway, and blocking its activity may promote an anti-tumour immune response. Nivolumab has a marketing authorisation for treating 'locally advanced or metastatic squamous 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 from the UK Medicines and Healthcare products Regulatory Agency. It is given intravenously.

2.2 The most common adverse reactions with nivolumab in clinical trials were tiredness, decreased appetite and nausea (occurring in more than 10% of people). The summary of product characteristics

notes that nivolumab is most commonly associated with immune-related adverse reactions, including pneumonitis, colitis, hepatitis, nephritis and kidney dysfunction, endocrinopathies and rash. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Nivolumab is available at a list price of £439 per 40-mg vial (excluding VAT; company submission). This equates to £2634 per dose, and £5268 per month, for a person weighing 73 kg. Costs may vary in different settings because of negotiated procurement discounts.

3 The company's submission

The Appraisal Committee (section 8) considered evidence submitted by Bristol-Myers Squibb and a review of this submission by the Evidence Review Group (ERG; section 9).

Clinical effectiveness

3.1 The company presented evidence from 1 randomised controlled trial, CheckMate-017. This was an international, open-label, phase III study in adults with squamous non-small-cell lung cancer (NSCLC) that had progressed during or after treatment with 1 platinum combination chemotherapy. Patients were randomised to have either nivolumab (n=135) or docetaxel (n=137), continued until disease progression or unacceptable toxicity occurred. The company stated that patient characteristics were well balanced between treatment groups. Results were analysed at a pre-planned interim analysis (December 2014) and a subsequent additional analysis; after the interim analysis, the trial was stopped because the primary end point had been met. Supportive evidence was presented from 3 non-randomised trials: CheckMate-063, CheckMate-003 and CheckMate-153.

3.2 In CheckMate-017, nivolumab was associated with statistically significant improvements in overall survival, progression-free survival and overall response rates, compared with docetaxel, at the interim analysis (Table 1). More mature results from the additional analysis also showed statistically significant improvements in these outcomes with nivolumab. The company also noted that in people whose disease responded, the duration of response was longer in the nivolumab group than in the docetaxel group. As allowed in the trial protocol, 28 patients in the nivolumab arm (20.7%) continued treatment beyond progression, of whom 9 (32.1%) benefited from continued treatment. Nivolumab also provided statistically significant improvements from baseline in quality of life, at most time points from week 12 onwards (assessed using the EuroQol EQ-5D visual analogue scale and utility index and the Lung Cancer Symptom Scale Average Symptom Burden Index). There were no significant changes from baseline in people having docetaxel. Pre-specified subgroup analyses based on patient and disease characteristics (for example, age, sex, performance status, previous therapies and time since diagnosis) and the proposed biological marker (expression of 'programmed cell death ligand 1', PD-L1) suggested that the effect of nivolumab on overall survival and progression-free survival was consistent across all subgroups.

Table 1 Clinical effectiveness outcomes in CheckMate-017 (interim analysis)

	Nivolumab (n=135)	**Docetaxel (n=137)**
Overall survival		
Median (95% CI), months	9.2 (7.3–13.3)	6.0 (5.1–7.3)
Hazard ratio (95% CI)	0.59 (0.44–0.79); p<0.001	
Overall survival at 12 months: % (95% CI)	42 (34–50)	24 (17–31)
Progression-free survival		

Median (95% CI), months	3.5 (2.1–4.9)	2.8 (2.1–3.5)
Hazard ratio (95% CI)	0.62 (0.47–0.81); p<0.001	
Progression-free survival at 12 months: % (95% CI)	21 (14–28)	6 (3–12)
Response rates		
Overall response rate: % (95% CI)	20 (14–28)	9 (5–15)
Time to response: median (range), months	2.2 (1.6–11.8)	2.1(1.8–9.5)
Abbreviations: CI, confidence interval; n, number of patients.		

3.3 The company compared the clinical effectiveness of nivolumab with erlotinib and best supportive care using an indirect comparison. The analysis was carried out in a Bayesian framework using a random-effects model, based on data from CheckMate-017 and 2 other trials identified in the systematic review (TAILOR: docetaxel compared with erlotinib; and Br.21: erlotinib compared with best supportive care). The results of the indirect comparison are academic in confidence and can't be reported here; the company stated that the indirect comparison suggested that nivolumab was associated with a statistically significant improvement in progression-free survival compared with erlotinib and in overall survival compared with best supportive care. The company highlighted differences between the trial populations, stating that it was not possible to control for this heterogeneity and so the results should be interpreted with caution.

3.4 The company presented adverse event data from CheckMate-017, -063, -003 and -153. The company reported that in CheckMate-017, nivolumab had a more favourable safety profile than docetaxel and was associated with fewer adverse effects; the most common adverse effects of nivolumab included fatigue, decreased appetite and asthenia. There were no deaths in the nivolumab group that were related to the study drug. The most common immune-related adverse effects associated with nivolumab that needed additional monitoring ('select adverse

events') included diarrhoea, pneumonitis, hypothyroidism and rash. The company stated that most of these effects were manageable and resolved using a defined treatment algorithm. The company stated that similar rates of adverse effects were seen in CheckMate-063, and that the safety data seen in CheckMate-153 were consistent with other clinical trials of nivolumab.

Cost effectiveness

3.5 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 model comprised 3 health states: progression free, progressed disease and death. The model used a cycle length of 1 week, a time horizon of 20 years (lifetime), and took the perspective of the NHS and personal social services. Costs and benefits were discounted at a rate of 3.5% per year.

3.6 The proportion of people in the each health state in each cycle was based on estimates of progression-free survival and overall survival, using a partitioned-survival (or 'area under the curve') approach. Short-term clinical trial data from CheckMate-017 (interim analysis) were extrapolated over the time horizon of the model. The company identified extrapolation models based on whether the proportional hazards assumption was met, goodness of fit, clinical plausibility, and internal and external validation: in the base case, overall survival was extrapolated using a log-logistic function, and progression-free survival was extrapolated using a 2-knot spline hazards model.

3.7 The company estimated quality of life by applying utility values to each health state. The utility scores were derived from EQ-5D utility

index data collected in CheckMate-017 (see section 3.2), before and after disease progression, valued using the UK value set: the utility scores in the progression-free and progressed-disease health states were 0.750 and 0.592 respectively. Quality of life was also affected by adverse effects, by applying utility decreases (decrements) for each effect with a severity grade of 3 or more and an incidence of at least 5% in either arm of CheckMate-017 (that is, dyspnoea, fatigue, asthenia, pneumonia, neutropenia and febrile neutropenia). The utility decrements ranged from 0.008 (pneumonia) to 0.09 (neutropenia).

3.8 The model incorporated costs in each health state, including acquisition and administration of nivolumab, docetaxel and any subsequent treatments (based on their list prices), managing adverse events, patient monitoring, disease management and care at the end of life. The costs were informed by estimates used in other technology appraisals (erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed following prior chemotherapy and nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer) and NHS reference costs.

3.9 In the company's base case, nivolumab was associated with total costs of £86,599, and a total of 1.3 quality-adjusted life years (QALYs), compared with £21,243 and 0.54 QALYs for docetaxel, giving an incremental cost-effectiveness ratio (ICER) of £85,950 per QALY gained.

3.10 The company’s deterministic sensitivity analysis showed that the model results were most sensitive to the hazard ratio for overall survival associated with nivolumab, average body weight and surface area, the discount rate for costs and outcomes, and the utility value in the progressed-disease state. In the probabilistic

sensitivity analysis, the additional costs associated with nivolumab increased by £3583 compared with the deterministic analysis, whereas the additional QALYs increased by 0.01. The probabilistic ICER therefore increased to £89,343 per QALY gained, and the probability that nivolumab was cost effective was less than 10% if the maximum acceptable ICER were £50,000 per QALY gained.

3.11 The company presented scenario analyses to explore the effect of assumptions about survival modelling, treatment discontinuation and optimising vial use to reduce wastage. Changing the extrapolation of overall survival to a 2-knot spline model substantially increased the ICER, whereas applying independent curves for progression-free survival to the nivolumab and docetaxel arm had a smaller effect. Applying a 1- or 2-year stopping rule or introducing vial optimisation all decreased the ICER associated with nivolumab, compared with the base case. The company also presented a scenario in which the cost effectiveness of nivolumab was compared with erlotinib (based on the erlotinib list price), in which nivolumab was associated with an ICER of £85,862 per QALY gained compared with erlotinib.

ERG's comments

3.12 The ERG stated that CheckMate-017 was a well-conducted trial, which captured relevant outcomes in a population that was generally similar to the population that would be seen in UK clinical practice. However, it noted some limitations in this trial – in particular, that the population excluded people with an Eastern Cooperative Oncology Group (ECOG) performance status greater than 1 and people taking high-dose steroids, who may be seen in clinical practice, and there was an unexpectedly high rate of withdrawal in the docetaxel arm. The ERG also noted that this trial had been stopped after the interim analysis, although it considered

that the more mature overall-survival data from the additional analysis (provided in the company's response to clarification) were consistent with the interim findings. The ERG commented that the progression-free survival data appeared skewed by the fact that the first radiological assessment of tumours took place after 9 weeks, so the proportional hazards assumption did not hold and the hazard ratio was not valid. However, the rates of progression-free survival at 12 months supported the clinical effectiveness of nivolumab.

3.13 The ERG noted that the evidence on health-related quality-of-life outcomes in CheckMate-017 was limited by low response rates. It expressed concern that people who continued to complete EQ-5D questionnaires may be those with the better health status. The ERG found that the number of people completing the EQ-5D correlated negatively with the mean score. The ERG also highlighted that in this trial, mean EQ-5D score increased rapidly over time after week 4, to a level higher than that reported by an age- and sex-matched sample from the UK general population.

3.14 The ERG highlighted heterogeneity in the studies included in the indirect treatment comparison, and also noted that there was not enough information in the TAILOR and Br.21 studies to confirm whether the proportional hazards assumption was met. The ERG therefore considered that, although the modelling approach was appropriate, the results of the indirect comparisons should be interpreted with caution and were unreliable. It stated that the clinical effectiveness of nivolumab compared with erlotinib and best supportive care remains unknown.

3.15 The ERG reviewed in detail the company's economic model, and commented that it was structured consistently with previous economic models for appraisals of cancer drugs, and was

implemented to a good standard. However, it identified 3 key areas of concern in the company's modelling:

- **Survival projections:** The ERG noted that the results of the model were highly sensitive to the methods used to project overall survival and progression-free survival. It highlighted that the log-logistic model for overall survival predicted that the risk of mortality would fall rapidly as time progressed (eventually to a level below that of the general population), implying that treatment with nivolumab would lead to a life-long reduction in the risk of death from any cause. It also expressed concerns about the methods used to model progression-free survival and the predicted benefits in post-progression free survival. The ERG noted that more than half of the survival gain associated with nivolumab in the company's model was accrued after disease progression; because most people stopped treatment on progression, this implies a substantial survival gain after nivolumab treatment was stopped. The ERG stated that there was no apparent difference in post-progression survival between nivolumab and docetaxel in CheckMate-017. The ERG considered that the company's methods of survival projection were inappropriate and had substantially overestimated the gains in overall, progression-free and post-progression survival associated with nivolumab.
- **Utility values:** The ERG acknowledged that the company had taken health state utility values from EQ-5D data collected in the CheckMate-017 trial. However, it emphasised the limitations in these data (see section 3.13). The ERG also considered that the disutilities associated with adverse events were unreliable because of limitations in the evidence on which they were based, the assumption that each patient with an adverse event only had 1 episode and that each episode only lasted 1 week.

The ERG considered that the effects of adverse events were underestimated, but this was not expected to have a substantial effect on the model results.

- **Treatment costs:** The ERG noted that to calculate drug costs, the company assumed that initial therapy continued until disease progression. However, this approach did not capture people who stopped treatment before progression (for example, because of adverse events), and in UK practice treatment with docetaxel is usually limited to a maximum of 4 doses. The ERG also highlighted that the company calculated drug dosages based on single estimates for average body weight and body surface area (rather than distributions), and used the list prices for all drugs rather than the average NHS cost for generic medicines, which is often lower. Finally, the ERG noted that the company assumed a different administration cost for docetaxel and nivolumab, but this was not necessary.

3.16 The ERG ran a series of exploratory analyses to address each of its concerns about the company's model. It proposed alternative approaches to model progression-free and overall survival, based on exponential models fitted from 2.2 months onwards (progression-free survival) and 40 weeks onwards (overall survival). The ERG also presented analyses using alternative health state utility values, of 0.65 in the progression-free state and 0.43 in the progressed-disease state, taken from a study by Nafees et al. (2008). It proposed that treatment costs may be more appropriately modelled using the time to treatment discontinuation data from CheckMate-017, a limit of 4 cycles of docetaxel, body weight and surface area distributions from a representative cohort of UK patients, and average NHS cost for generic drugs taken from the Commercial Medicines Unit's Electronic Market Information Tool (eMIT). The results of the ERG's analyses are presented in

Table 2; the ERG presented a 'revised analysis' based on its preferred changes to the company model, in which the ICER for nivolumab compared with docetaxel was £132,989 per QALY gained.

Table 2 ERG's exploratory analyses

Model scenario	Nivolumab versus docetaxel			*Change versus company base case ICER*
	Incremental cost	**Incremental QALYs**	**ICER (£/QALY gained)**	
Company's base case	**£65,355**	**0.76**	**£85,950**	-
1) ERG progression-free survival estimates	£50,434	0.73	£68,912	*−£17,038*
2) ERG overall estimates	£60,366	0.46	£131,979	*+£46,029*
3) Revised costs of nivolumab and docetaxel	£69,854	0.76	£91,867	*+£5,917*
4) Revised costs of subsequent chemotherapy drugs	£65,539	0.76	£86,192	*+£241*
5) Same administration cost for nivolumab and docetaxel	£63,089	0.76	£82,970	*−£2,981*
6) Docetaxel limited to 4 cycles	£68,559	0.76	£90,164	*+£4,213*
7) Drugs given at the start of cycles	£65,891	0.76	£86,654	*+£704*
8) Duration based on time to treatment discontinuation	£49,837	0.76	£65,542	*−£20,409*
9) Alternative utility scores	£65,355	0.62	£105,915	*+£19,964*
ERG revised analysis: Company base case plus changes 1–6, 8 and 9 (above)	**£47,512**	**0.36**	**£132,989**	*+£47,039*

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

3.17 Full details of all the evidence are in the Committee papers.

4 Consideration of the evidence

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.

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 would be 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. In light of this, 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.

4.2 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 that there are few alternatives. The Committee concluded that there is an important unmet need for people with squamous NSCLC whose disease has progressed after chemotherapy.

Clinical effectiveness

4.3 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 4.1), 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 in this trial, nivolumab provided significant gains in both progression-free survival and overall survival, compared with docetaxel (see section 3.2). 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 acknowledged 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. Based on the gains in overall and progression-free survival seen in the CheckMate-017 trial, and taking into account the clinical experts'

statements, the Committee concluded that nivolumab is a clinically effective treatment option for previously treated squamous NSCLC.

4.4 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 worse performance statuses were excluded from the trial (see section 3.12), 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.

4.5 The Committee noted that the company presented pre-specified subgroup analysis from CheckMate-017, based on patient and disease characteristics and the proposed biological marker (PD-L1 expression; see section 3.2). It noted that the scope for this appraisal stated that if the evidence allows, consideration will be given to subgroups based on biological markers. The Committee therefore considered whether there were any people or groups of people for whom nivolumab may be particularly effective or beneficial. It noted that the subgroup analyses in CheckMate-017 provided no evidence of a significantly different effect in any of the subgroups assessed, including the proposed biomarker. The Committee highlighted that PD-L1 expression status was measured in either fresh or archived tissue samples, but that this marker is dynamic and can change over time; it therefore considered that these results should be viewed with caution. It heard from the clinical experts that the identification of subgroups who may benefit particularly from nivolumab is an area of active research, but the Committee did not see any additional evidence beyond that presented by the company. The Committee concluded that it was

not possible to identify any subgroups for whom nivolumab would provide particular benefits, and so it was unable to make recommendations for nivolumab in specific subgroups.

Cost effectiveness

4.6 The Committee considered the cost-effectiveness evidence presented by the company 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 overall survival and progression-free survival, the utility scores and the treatment costs.

Extrapolation of overall survival and progression-free survival

4.7 The Committee understood that the company's model and the ERG's exploratory analyses were based on different approaches to extrapolate progression-free survival beyond the point at which data from the trial were available. It noted that the company had used the whole dataset to project progression-free survival to the longer term; it understood that the company considered that its extrapolation model was appropriate based on the goodness of fit, the fact that the proportional hazards assumption was not met, clinical plausibility and internal and external validation. It heard from the ERG that using the full dataset may have led to the early section of the curves influencing the long-term extrapolation. The ERG highlighted that the first radiological assessment of tumour progression in the trial was done after 3 months of treatment, and that before this point the progression-free survival curves for nivolumab and docetaxel were very similar; the ERG considered that the true treatment effect at this point may have been masked, so disregarded the early section of the curves in its exploratory

analysis. The Committee understood that the ERG had therefore based its extrapolation on the curves only after the point at which they began to diverge (2.2 months), reflecting this hypothesis. The company expressed concerns that the ERG may not have used the latest data to inform its exploratory analysis, and that this could have underestimated the progression-free survival gain. The Committee observed that decreasing the progression-free survival gain associated with nivolumab (compared with docetaxel) led to a decrease in the incremental cost-effectiveness ratio (ICER); consequently, it was aware that if the company's concern was correct and the ERG had underestimated the progression-free survival gain, the ICER would be higher than predicted by the ERG. The Committee acknowledged the company's concern, and stated that it is important to ensure the latest data are used in all analyses. The Committee considered that it agreed with the ERG's rationale for its approach, and concluded that the ERG's approach to extrapolating progression-free survival was appropriate.

4.8 The Committee noted that the company's modelling of overall survival 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 understood the company's justification for the extrapolation approach, but queried the clinical plausibility of the results predicted by this approach. It noted that most of the overall-survival gain was accrued after disease progression when treatment with nivolumab has stopped, suggesting a long benefit after treatment that is greater than the benefit during treatment. The Committee considered that a small gain in survival after disease progression was plausible, based on comments from the clinical experts, but that the size of the gain implied by the company's model was not plausible or supported by the clinical trial evidence.

The Committee also understood that the model predicted that mortality risk would decrease over time. It observed that this implied people would be at a lower risk of dying from any cause as they got older, and that after 18 years they would reach a lower risk of death than people of the same age from the general population. The Committee understood that nivolumab may well provide important long-term survival benefits for some people (see section 4.3), but considered that it was not plausible that a person who has been treated with a chemotherapy regimen followed by nivolumab for metastatic NSCLC would have a lower risk of death than a person of the same age without NSCLC. The Committee therefore reviewed the ERG's exploratory analysis of overall survival. It noted that the ERG's analysis also predicted a survival gain after disease progression, but that this gain was both smaller in size and a smaller proportion of the total overall-survival gain than predicted by the company. Because the results from company's extrapolation were not clinically plausible, and the ERG's analysis appeared to mitigate some of the limitations in the company's results, the Committee concluded that the ERG's modelling of overall survival was more appropriate for its decision-making.

Utility values

4.9 The Committee was pleased to note 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 base case, the utility values in the progression-free and progressed-disease states were 0.750 and 0.592 respectively. However, the Committee also noted limitations in this evidence. It considered that the negative correlation between EQ-5D score and the number of responders (see section 3.13) strongly suggested

that the results were influenced by selection bias, that is, the people who responded to 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 (see section 3.13). 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 further called into question 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 the appraisal of erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed following prior chemotherapy, 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 state and 0.43 in the progressed-disease 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 EQ-5D. 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 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.

4.10 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 on 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 understood that the adverse effect disutilities were unlikely to have an important impact on the economic model results. It concluded that adverse effects had been adequately captured in the model.

Treatment costs

4.11 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; see section 3.2). The Committee understood that the company had estimated the duration of treatment based on the assumption that people continued 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 discontinuation because of adverse events. The Committee concluded that because the ERG had used

the treatment duration data from the trial and had captured treatment beyond progression as well as discontinuation as a result of adverse events, the ERG's approach to modelling treatment duration was appropriate.

4.12 The Committee noted the ERG's comment that docetaxel therapy is usually limited to a maximum of 4 cycles in clinical practice, 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 company's approach of not limiting docetaxel to a maximum of 4 cycles in the economic model was appropriate in this case.

4.13 The Committee noted that 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 a different administration cost 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, in which the ERG used its preferred approaches for these assumptions (see section 3.16), were appropriate.

Conclusions

4.14 The Committee heard from the company, clinical experts and patient experts that they consider nivolumab to be an innovative treatment option, both in its therapeutic approach and its clinical effectiveness. It understood that nivolumab was awarded a 'promising innovative medicine' designation and was approved through the early access to medicines scheme from the UK Medicines and Healthcare products Regulatory Agency. 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.

4.15 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met.

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

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

4.16 The Committee noted the evidence presented by the company, which showed that people with 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 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, and that this was 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.

4.17 The Committee considered the most plausible ICER for nivolumab, compared with docetaxel. It noted that the company's base case ICER was £86,000 per QALY gained, whereas the ICER in the ERG's revised analysis, with all of the proposed changes included, was £133,000 per QALY gained (see sections 3.9 and 3.16). The Committee recalled that it considered most of the ERG's changes appropriate – in particular, extrapolating progression-free and overall survival, the modelling of treatment duration and the amended drug costs (see sections 4.7, 4.8, 4.11 and 4.13). Conversely, the Committee considered that the company's approach of not limiting the duration of docetaxel therapy was appropriate (see section 4.12). It noted that when the ERG had limited docetaxel treatment to 4 cycles, the ICER had increased by

£4210 per QALY gained compared with the company's base case; the Committee therefore considered that removing this assumption from the ERG's revised analysis was likely to reduce the ICER by a similar amount. The Committee also considered that both the company's and ERG's utility values had limitations, and that the most appropriate utility values would be between the 2 sets (see section 4.9). The Committee noted that incorporating the ERG's utility values into the company's base case had increased the ICER by £20,000 per QALY gained, and so changing to utility values between the company's and ERG's values would reduce the ICER by up to this amount compared with the ERG's revised analysis. The Committee therefore considered that the combined effect of removing the limit on the duration of docetaxel treatment and using the most appropriate utility values would be to reduce the ICER by between £4000 and £24,000 per QALY gained, compared with the ERG's revised analysis. It concluded that the most plausible ICER for nivolumab compared with docetaxel would be between £109,000 and £129,000 per QALY gained. Although it was aware that nivolumab was innovative and met the criteria to be considered a life-extending, end-of-life treatment, the Committee did not recommend nivolumab as a cost-effective use of NHS resources.

4.18 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 acknowledged '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 irrelevant for considering the cost effectiveness of

nivolumab for treating locally advanced or metastatic squamous NSCLC after prior chemotherapy.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title:	Section
Key conclusion		
Nivolumab is not recommended within its marketing authorisation for treating locally advanced or metastatic squamous non-small-cell lung cancer (NSCLC) after prior chemotherapy in adults.		1.1
• The Committee considered that nivolumab is a clinically effective treatment option for previously treated squamous NSCLC.		4.3
• However, the most plausible incremental cost-effectiveness ratio (ICER) for nivolumab compared with docetaxel is between £109,000 and £129,000 per quality-adjusted life year (QALY) gained.		4.17
• Although nivolumab was innovative and met the criteria to be considered a life-extending, end-of-life treatment, the Committee did not recommend nivolumab as a cost-effective use of NHS resources.		4.17

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 progressed after chemotherapy.	4.2
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee heard from the company, clinical experts and patient experts that they consider nivolumab to be innovative, both in therapeutic approach and clinical effectiveness. Nivolumab was awarded a 'promising innovative medicine' designation and was approved through the early access to medicines scheme from the UK Medicines and Healthcare products Regulatory Agency.	4.14

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.	4.1
Adverse reactions	The company reported that nivolumab had a more favourable safety profile than docetaxel and was associated with fewer adverse effects, the most common of which included fatigue, decreased appetite and asthenia. The most common immune-related adverse effects associated with nivolumab included diarrhoea, pneumonitis, hypothyroidism and rash.	3.4
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The company presented evidence from 1 randomised controlled trial (CheckMate-017) and 3 non-randomised trials (CheckMate-063, -003 and -153). The ERG stated that CheckMate-017 was well conducted and captured relevant outcomes, although it also noted some limitations in this trial.	3.1 3.12

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.	4.4
Uncertainties generated by the evidence	The ERG noted that the evidence on health-related quality-of-life outcomes was limited by low response rates. The Committee also noted limitations in this evidence. The ERG highlighted limitations in the company's indirect treatment comparison, and stated that the clinical effectiveness of nivolumab compared with erlotinib and best supportive care remains unknown.	3.13, 4.9 3.14
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee noted that the company presented subgroup analysis based on patient and disease characteristics and the proposed biological marker (PD-L1 expression), but noted that these analyses provided no evidence of a significantly different effect. It heard from the clinical experts that the identification of subgroups who may benefit particularly from nivolumab is an area of active research. The Committee concluded that it was not possible to identify any subgroups for whom nivolumab would provide particular benefits.	4.5

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 ERG's economic analyses were both much more than 3 months (15.7 months and 7.17 months respectively).	3.2 Table 1, 4.16
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.	3.5
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee considered 3 key areas of concern about the company's economic model: Extrapolation of overall survival and progression-free survival: • The company and ERG took different approaches to extrapolate progression-free survival. The Committee agreed with the ERG's rationale, and concluded that the ERG's approach was appropriate. • The Committee considered that the	4.6–4.13

	company's modelling of overall survival was not plausible, but the ERG's modelling appeared to mitigate some of the limitations in the company's results and so was more appropriate for decision-making. Utility values: • The Committee considered that there were limitations in the utility values presented by both the company and the ERG. 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. Treatment costs: • The Committee noted that the ERG's exploratory analysis of treatment duration was based on time to treatment discontinuation data from the trial and accounted for treatment beyond progression as well as discontinuation because of adverse events; it concluded that this approach was appropriate. • The Committee noted concerns about the use of body weight estimates, list prices and administration costs in the company's model, and considered that the ERG's exploratory analyses were appropriate.	

Incorporation of health-related quality-of-life benefits and utility values	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.	3.7
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 ERG presented exploratory analyses using alternative health state utility values (of 0.65 and 0.43 respectively) taken from a study by Nafees et al. (2008).	3.16
	The Committee considered that there were limitations in the utility values presented by both the company and the ERG.	4.9
	The Committee considered that there were no additional benefits associated with nivolumab that had not been captured in the economic analysis.	4.14
Are there specific groups of people for whom the technology is particularly cost effective?	The Committee concluded that it was unable to make recommendations for specific subgroups.	4.5

What are the key drivers of cost effectiveness?	The company showed that the model results were most sensitive to the hazard ratio for overall survival associated with nivolumab, average body weight and surface area, the discount rate for costs and outcomes, and the utility value in the progressed-disease state.	3.10
Most likely cost-effectiveness estimate (given as an ICER)	The Committee concluded that the most plausible ICER for nivolumab compared with docetaxel would be between £109,000 and £129,000 per QALY gained.	4.17
Additional factors taken into account		
Patient access schemes (PPRS)	None	–
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 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.	4.16

	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 Implementation

5.1 NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the NICE website.

Published

- Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer. NICE technology appraisal guidance 347 (2015).
- Suspected cancer: recognition and referral. NICE guideline NG12 (2015).
- Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer. NICE technology appraisal guidance 310 (2014).
- Crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene. NICE technology appraisal guidance 296 (2013).
- Lung cancer in adults. NICE quality standard 17 (2012).
- Lung cancer: diagnosis and management. NICE guideline CG121 (2011).
- Erlotinib for the treatment of non-small-cell lung cancer. NICE technology appraisal guidance 162 (2008).
- Pemetrexed for the treatment of non-small-cell lung cancer. NICE technology appraisal guidance 124 (2007).

Under development

- Ceritinib for previously treated anaplastic lymphoma kinase-positive non-small-cell lung cancer. NICE technology appraisal guidance, publication expected January 2016.
- Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer. NICE technology appraisal guidance, publication expected August 2016.
- Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer. NICE technology appraisal guidance, publication expected September 2016.

- Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed following prior chemotherapy (Review of TA162 and TA175). NICE technology appraisal guidance, publication date to be confirmed.
- Necitumumab for untreated advanced, metastatic, squamous non-small-cell lung cancer. NICE technology appraisal guidance, publication expected September 2016.
- Pembrolizumab for treating advanced or recurrent PD-L1 positive non-small-cell lung cancer after progression with platinum-based chemotherapy. NICE technology appraisal guidance, publication date to be confirmed.

7 Proposed date for review of guidance

7.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Professor Andrew Stevens
Chair, Appraisal Committee
December 2015

8 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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.

Professor Andrew Stevens
Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Professor Eugene Milne
Vice Chair of Appraisal Committee C, Director of Public Health, City of Newcastle upon Tyne

Mr David Chandler
Lay Member

Mrs Gail Coster
Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

Professor Peter Crome

Honorary Professor, Department of Primary Care and Population Health, University College London

Dr Nigel Langford

Consultant in Clinical Pharmacology and Therapeutics and Acute Physician, Leicester Royal Infirmary

Dr Patrick McKiernan

Consultant Pediatrician, Birmingham Children's Hospital

Dr Andrea Manca

Health Economist and Senior Research Fellow, University of York

Dr Iain Miller

Founder & Chief Executive Officer, Health Strategies Group

Dr Anna O'Neill

Deputy Head of Nursing & Health Care School / Senior Clinical University Teacher, University of Glasgow

Dr Claire Rothery

Research Fellow in Health Economics, University of York

Professor Peter Selby

Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Professor Matt Stevenson

Technical Director, School of Health and Related Research, University of Sheffield

Professor Robert Walton

Clinical Professor of Primary Medical Care, Barts and The London School of Medicine and Dentistry

Dr Judith Wardle

Lay Member

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

Technical Lead

Joanne Holden

Technical Adviser

Lori Farrar / Stephanie Yates

Project Managers

9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Liverpool Reviews and Implementation Group:

- Fleeman N, Bagust A, Richardson M et al. Nivolumab for previously treated locally advanced or metastatic squamous-cell non-small cell lung cancer [ID811]: A Single Technology Appraisal. LR*i*G, University of Liverpool, October 2015

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to make written

submissions. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- Bristol-Myers Squibb

II. Professional/expert and patient/carer groups:

- Roy Castle Lung Cancer Foundation
- Association of Cancer Physicians
- British Thoracic Oncology Group
- British Thoracic Society
- Cancer Research UK
- National Lung Cancer Forum for Nurses
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- Royal College of Radiologists

III. Other consultees:

- Department of Health
- NHS England
- NHS Halton Clinical Commissioning Group
- NHS Lewisham Clinical Commissioning Group
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Care Quality Commission
- Department of Health, Social Services and Public Safety for Northern Ireland

- Healthcare Improvement Scotland
- Roche Products
- Institute of Cancer Research
- National Cancer Research Institute
- Public Health England
- Public Health Wales

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on Nivolumab for treating metastatic, squamous, non-small-cell lung cancer after chemotherapy by attending the initial Committee discussion and providing a written statement to the Committee. They are invited to comment on the ACD.

- Matthew Hatton, Consultant Clinical Oncologist, nominated by NCRI/RCP/RCR/ACP/BTOG – clinical expert
- Sanjay Popat, Consultant Thoracic Medical Oncologist, nominated by Bristol-Myers Squibb and NCRI/RCP/RCR/ACP/BTOG – clinical expert
- Carol Davies, Macmillan Lung Cancer Specialist Nurse, nominated by National Lung Cancer Forum for Nurses - patient expert

E. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Bristol-Myers Squibb